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(12) (19) (CA) **Demande-Application**

(21) (A1) **2,271,718**
(86) 1997/11/13
(87) 1998/05/22

(72) HARRINGTON, Lea A., CA
(72) ROBINSON, Murray O., US
(71) AMGEN INC., US
(71) AMGEN CANADA INC., CA

(51) Int.Cl.^{6} C12N 15/54, C12N 15/85, A61K 31/70, A01K 67/027, C12Q 1/68, C12Q 1/48, A61K 38/45, C07K 16/40, C12N 1/21, C12N 1/19, C12N 9/12, C12N 15/11
(30) 1996/11/15 (08/751,189) US
(30) 1997/06/11 (08/873,039) US
(30) 1997/10/16 (08/951,733) US

(54) **GENES CODANT DES PROTEINES DE TELOMERASE**
(54) **GENES ENCODING TELOMERASE PROTEINS**

(57) L'invention concerne des molécules d'acide nucléique, qui codent des polypeptides du complexe télomérase. L'invention se rapporte également à des procédés de préparation desdites molécules d'acide nucléique et desdits polypeptides et à des procédés d'utilisation desdites molécules.

(57) Disclosed are nucleic acid molecules encoding polypeptides of the telomerase complex. Also disclosed are methods of preparing the nucleic acid molecules and polypeptides, and methods of using these molecules.

CA 02271718 1999-05-13

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/54, 9/12, C12Q 1/68, 1/48, C12N 15/11, 15/85, A01K 67/027, C07K 16/40, A61K 38/45, 31/70, C12N 1/21, 1/19

A1

(11) International Publication Number: WO 98/2134

(43) International Publication Date: 22 May 1998 (22.05.98

(21) International Application Number: PCT/US97/21248

(22) International Filing Date: 13 November 1997 (13.11.97)

(30) Priority Data:

08/871,189	15 November 1996 (15.11.96)	US
08/873,039	11 June 1997 (11.06.97)	US
08/951,733	16 October 1997 (16.10.97)	US

(71) Applicants: AMGEN INC. [US/US]; Amgen Center, 1840 De Havilland Drive, Thousand Oaks, CA 91320-1789 (US). AMGEN CANADA INC. [CA/CA]; Suite 303, 6733 Mississauga Road, Mississauga, Ontario L5N 6J5 (CA).

(72) Inventors: HARRINGTON, Lea, A.; 55 Pears Avenue, Toronto, Ontario M5R 1S9 (CA). ROBINSON, Murray, O.; 22623 Pacific Coast Highway, Malibu, CA 90265 (US).

(74) Agents: ODRE, Steven, M. et al.; Amgen, Inc., Amgen Center, 1840 De Havilland Drive, Thousand Oaks, CA 91320-1789 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM) European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.
With amended claims and statement.

Date of publication of the amended claims and statement: 30 July 1998 (30.07.9

(54) Title: GENES ENCODING TELOMERASE PROTEINS

(57) Abstract

Disclosed are nucleic acid molecules encoding polypeptides of the telomerase complex. Also disclosed are methods of preparing th nucleic acid molecules and polypeptides, and methods of using these molecules.

AMENDED CLAIMS

[received by the International Bureau on 19 June 1998 (19.06.98); new claims 33-56 added; remaining claims unchanged (7 pages)]

1. A TP2 nucleic acid molecule encoding a polypeptide selected from the group consisting of:

(a) the nucleic acid molecule of SEQ ID NO:13;

(b) the nucleic acid molecule that is nucleotides 1920-2820 of SEQ ID NO:13;

(c) the nucleic acid molecule of SEQ ID NO:19

(d) a nucleic acid molecule encoding the polypeptide of SEQ ID NO:14, or a biologically active fragment thereof;

(e) a nucleic acid molecule encoding the polypeptide of SEQ ID NO:20, or a biologically active fragment thereof;

(f) a nucleic acid molecule that encodes a polypeptide that is at least 90 percent identical to the polypeptide of SEQ ID NO:14;

(g) a nucleic acid molecule that encodes a polypeptide that is at least 90 percent identical to the polypeptide of SEQ ID NO:20;

(h) a nucleic acid molecule that hybridizes under stringent conditions to any of (a)-(g) above; and

(i) a nucleic acid molecule that is the complement of any of (a)-(g) above.

2. The nucleic acid molecule that is SEQ ID NO:13 or SEQ ID NO:19.

3. The nucleic acid molecule that is nucleotides 1920-2820 of SEQ ID NO:13.

4. A nucleic acid molecule encoding the polypeptide of SEQ ID NO:14 of SEQ ID NO:20.

5. A nucleic acid molecule selected from the group consisting of: nucleotides 1-1689 of SEQ ID NO:13, nucleotides 1-1920 of SEQ ID NO:13, nucleotides 1920-2820 of SEQ ID NO:13, nucleotides 2089-2820 of SEQ ID NO:13, and nucleotides 2089-2859 of SEQ ID NO:13.

6. A nucleic acid molecule encoding amino acids 640-940 of the polypeptide of SEQ ID NO:14.

7. A vector comprising the nucleic acid molecule of claim 1.

8. A vector comprising the nucleic acid molecule of claim 2.

9. A vector comprising the nucleic acid molecule of claim 3.

10. A vector comprising the nucleic acid molecule of claim 4.

11. A vector comprising the nucleic acid molecule of claim 5.

12. A vector comprising the nucleic acid molecule of claim 6.

13. A host cell comprising the vector of claim 7.

14. A host cell comprising the vector of claim 8.

15. A host cell comprising the vector of claim 9.

16. A host cell comprising the vector of claim 10.

17. A host cell comprising the vector of claim 11.

18. A host cell comprising the vector of claim 12.

19. A process for producing a TP2 polypeptide comprising the steps of:

(a) expressing a polypeptide encoded by the nucleic acid of claim 1 in a suitable host; and

(b) isolating the polypeptide.

20. The process of claim 19 wherein the polypeptide is SEQ ID NO:14 or SEQ ID NO:20.

21. The process of claim 19 wherein the polypeptide is amino acids 640-940 of SEQ ID NO:14.

22. A TP2 polypeptide selected from the group consisting of:

(a) the polypeptide of SEQ ID NO:14;

(b) the polypeptide that is amino acids 640-940 of SEQ ID NO:14;

(c) the polypeptide of SEQ ID NO:20; and

(d) a polypeptide that is at least 90 percent identical to any of the polypeptides of (a)-(c).

23. A TP2 polypeptide that is the polypeptide of SEQ ID NO:14, SEQ ID NO:20, or a biologically active fragment thereof.

24. A TP2 polypeptide selected from the group consisting of: amino acids 1-563 of SEQ ID NO:14; amino acids 1-640 of SEQ ID NO:14; amino acids 640-940 of SEQ ID NO:14; amino acids 696-940 of SEQ ID NO:14; and amino acids 696-953 of SEQ ID NO:14.

25. The TP2 polypeptide of claim 22 that does not possess an amino terminal methionine.

26. A method of increasing proliferation of a cell, comprising expressing a nucleic acid encoding TP2 or a biologically active fragment thereof, in the cell.

27. A method of increasing telomerase activity in a cell, comprising expressing a TP2 gene, or a biologically active fragment thereof, in the cell.

28. A method of decreasing telomerase in a cell, comprising expressing a TP2 mutant in a cell, wherein the mutant does not have TP2 biological activity.

29. A nucleic acid molecule encoding a mutant TP2 polypeptide, wherein the codon for aspartic acid at amino acid position 868 or 869 is changed to a codon for alanine.

30. A nucleic acid molecule encoding a mutant TP2 polypeptide, wherein the codons for aspartic acid at amino acid positions 868 and 869 are changed to codons for alanine.

31. A polypeptide encoded by the nucleic acid molecule of claim 29.

32. A polypeptide encoded by the nucleic acid molecule of claim 30.

33. A TRIP1 nucleic acid molecule encoding a polypeptide selected from the group consisting of:

(a) the nucleic acid molecule of SEQ ID NO:1;

(b) the nucleic acid molecule of SEQ ID NO:2;

(c) a nucleic acid molecule encoding the polypeptide of SEQ ID NO:3, SEQ ID NO:4, or a biologically active fragment thereof;

(d) a nucleic acid molecule that encodes a polypeptide that is at least 70 percent identical to the polypeptide of SEQ ID NO:3 or SEQ ID NO:4;

(e) a nucleic acid molecule that hybridizes under stringent conditions to any of (a)-(d) above; and

(f) a nucleic acid molecule that is the complement of any of (a)-(e) above.

34. The nucleic acid molecule that is SEQ ID NO:1.

35. The nucleic acid molecule that is SEQ ID NO:2.

36. A nucleic acid molecule encoding the polypeptide of SEQ ID NO:3.

37. A nucleic acid molecule encoding the polypeptide of SEQ ID NO:4.

38. A nucleic acid molecule encoding amino acids 1-871 of the polypeptide of SEQ ID NO:3.

39. A vector comprising the nucleic acid molecule of claim 33.

40. A vector comprising the nucleic acid molecule of claim 34.

41. A vector comprising the nucleic acid molecule of claim 35.

42. A vector comprising the nucleic acid molecule of claim 36.

43. A vector comprising the nucleic acid molecule of claim 37.

44. A vector comprising the nucleic acid molecule of claim 38.

45. A host cell comprising the vector of claim 39.

46. A host cell comprising the vector of claim 40.

47. A host cell comprising the vector of claim 41.

48. A host cell comprising the vector of claim 42.

49. A host cell comprising the vector of claim 43.

50. A host cell comprising the vector of claim 44.

51. A process for producing a TRIP1 polypeptide comprising the steps of:

(a) expressing a polypeptide encoded by the nucleic acid of claim 1 in a suitable host; and

(b) isolating the polypeptide.

52. The process of claim 51 wherein the polypeptide is SEQ ID NO:3.

53. The process of claim 51 wherein the polypeptide amino acids 1-871 of SEQ ID NO:3.

54. A TRIP1 polypeptide selected from the group consisting of:

(a) the polypeptide of SEQ ID NO:3;

(b) the polypeptide that is amino acids 1-871 of SEQ ID NO:3; and

(c) a polypeptide that is at least 70 percent identical to the polypeptide of (a) or (b).

55. A TRIP1 polypeptide that is the polypeptide of SEQ ID NO:3 or a biologically active fragment thereof.

56. The TRIP1 polypeptide of claim 52 that does not possess an amino terminal methionine.

STATEMENT UNDER ARTICLE 19

The claims of International Application WO 98/21248, published 22 May 1998, have been amended. Original claims 1 through 32 have not been amended, however, new claims 33 through 56 have been added. Claims 33 through 56 are directed to an aspect of the invention not originally claimed by Applicants. Specifically, claims 33 through 56 encompass telomerase protein 1 and DNA encoding therefor. Such claims are fully supported by the written description and the drawings.

FIG. 1A

ATGGAAAAACTCCATGGGCATGTGTCTGCCCATCCAGACATCCTCTCCT
TGGAGAACCGGTGCCTGGCTATGCTCCCTGACTTACAGCCCTTGGAGAA
ACTACATCAGCATGTATCTACCCACTCAGATATCCTCTCCTTGAAGAAC
CAGTGCCTAGCCACGCTTCCTGACCTGAAGACCATGGAAAAACCACATG
GATATGTGTCTGCCCACCCAGACATCCTCTCCTTGGAGAACCAGTGCCT
GGCCACACTTTCTGACCTGAAGACCATGGAGAAACCACATGGACATGTT
TCTGCCCACCCAGACATCCTCTCCTTGGAGAACCGGTGCCTGGCCACCC
TCCCTAGTCTAAAGAGCACTGTGTCTGCCAGCCCCTTGTTCCAGAGTCT
ACAGATATCTCACATGACGCAAGCTGATTTGTACCGTGTGAACAACAGC
AATTGCCTGCTCTCTGAGCCTCCAAGTTGGAGGGCTCAGCATTTCTCTA
AGGGACTAGACCTTTCAACCTGCCCTATAGCCCTGAAATCCATCTCTGC
CACAGAGACAGCTCAGGAAGCAACTTTGGGTCGTTGGTTTGATTCAGAA
GAGAAGAAAGGGGCAGAGACCCAAATGCCTTCTTATAGTCTGAGCTTGG
GAGAGGAGGAGGAGGTGGAGGATCTGGCCGTGAAGCTCACCTCTGGAGA
CTCTGAATCTCATCCAGAGCCTACTGACCATGTCCTTCAGGAAAAGAAG
ATGGCTCTACTGAGCTTGCTGTGCTCTACTCTGGTCTCAGAAGTAAACA
TGAACAATACATCTGACCCCACCCTGGCTGCCATTTTTGAAATCTGTCG
TGAACTTGCCCTCCTGGAGCCTGAGTTTATCCTCAAGGCATCTTTGTAT
GCCAGGCAGCAGCTGAACGTCCGGAATGTGGCCAATAACATCTTGGCCA

FIG.1B

TTGCTGCTTTCTTGCCGGCGTGTCGCCCCCACCTGCGACGATATTTCTG

TGCCATTGTCCAGCTGCCTTCTGACTGGATCCAGGTGGCTGAGCTTTAC

CAGAGCCTGGCTGAGGGAGATAAGAATAAGCTGGTGCCCCTGCCCGCCT

GTCTCCGTACTGCCATGACGGACAAATTTGCCCAGTTTGACGAGTACCA

GCTGGCTAAGTACAACCCTCGGAAGCACCGGGCCAAGAGACACCCCCGC

CGGCCACCCCGCTCTCCAGGGATGGAGCCTCCATTTTCTCACAGATGTT

TTCCAAGGTACATAGGGTTTCTCAGAGAAGAGCAGAGAAAGTTTGAGAA

GGCCGGTGATACAGTGTCAGAGAAAAAGAATCCTCCAAGGTTCACCCTG

AAGAAGCTGGTTCAGCGACTGCACATCCACAAGCCTGCCCAGCACGTTC

AAGCCCTGCTGGGTTACAGATACCCCTCCAACCTACAGCTCTTTTCTCG

AAGTCGCCTTCCTGGGCCTTGGGATTCTAGCAGAGCTGGGAAGAGGATG

AAGCTGTCTAGGCCAGAGACCTGGGAGCGGGAGCTGAGCCTACGGGGGA

ACAAAGCGTCGGTCTGGGAGGAACTCATTGAAAATGGGAAGCTTCCCTT

CATGGCCATGCTTCGGAACCTGTGCAACCTGCTGCGGGTTGGAATCAGT

TCCCGCCACCATGAGCTCATTCTCCAGAGACTCCAGCATGGGAAGTCGG

TGATCCACAGTCGGCAGTTTCCATTCAGATTTCTTAACGCCCATGATGC

CATTGATGCCCTCGAGGCTCAACTCAGAAATCAAGCATTGCCCTTTCCT

TCGAATATAACACTGATGAGGCGGATACTAACTAGAAATGAAAAGAACC

GTCCCAGGCGGAGGTTTCTTTGCCACCTAAGCCGTCAGCAGCTTCGTAT

FIG.1C

GGCAATGAGGATACCTGTGTTGTATGAGCAGCTCAAGAGGGAGAAGCTG
AGAGTACACAAGGCCAGACAGTGGAAATATGATGGTGAGATGCTGAACA
GGTACCGACAGGCCCTAGAGACAGCTGTGAACCTCTCTGTGAAGCACAG
CCTGCCCCTGCTGCCAGGCCGCACTGTCTTGGTCTATCTGACAGATGCT
AATGCAGACAGGCTCTGTCCAAAGAGCAACCCACAAGGGCCCCCGCTGA
ACTATGCACTGCTGTTGATTGGGATGATGATCACGAGGGCGGAGCAGGT
GGACGTCGTGCTGTGTGGAGGTGACACTCTGAAGACTGCAGTGCTTAAG
GCAGAAGAAGGCATCCTGAAGACTGCCATCAAGCTCCAGGCTCAAGTCC
AGGAGTTTGATGAAAATGATGGATGGTCCCTGAATACTTTTGGGAAATA
CCTGCTGTCTCTGGCTGGCCAAAGGGTTCCTGTGGACAGGGTCATCCTC
CTTGGCCAAAGCATGGATGATGGAATGATAAATGTGGCCAAACAGCTTT
ACTGGCAGCGTGTGAATTCCAAGTGCCTCTTTGTTGGTATCCTCCTAAG
AAGGGTACAATACCTGTCAACAGATTTGAATCCCAATGATGTGACACTC
TCAGGCTGTACTGATGCGATACTGAAGTTCATTGCAGAGCATGGGGCCT
CCCATCTTCTGGAACATGTGGGCCAAATGGACAAAATATTCAAGATTCC
ACCACCCCCAGGAAAGACAGGGGTCCAGTCTCTCCGGCCACTGGAAGAG
GACACTCCAAGCCCCTTGGCTCCTGTTTCCCAGCAAGGATGGCGCAGCA
TCCGGCTTTTCATTTCATCCACTTTCCGAGACATGCACGGGGAGCGGGA
CCTGCTGCTGAGGTCTGTGCTGCCAGCACTGCAGGCCCGAGCGGCCCCT

FIG.1D

CACCGTATCAGCCTTCACGGAATCGACCTCCGCTGGGGCGTCACTGAGG

AGGAGACCCGTAGGAACAGACAACTGGAAGTGTGCCTTGGGGAGGTGGA

GAACGCACAGCTGTTTGTGGGGATTCTGGGCTCCCGTTATGGATACATT

CCCCCCAGCTACAACCTTCCTGACCATCCACACTTCCACTGGGCCCAGC

AGTACCCTTCAGGGCGCTCTGTGACAGAGATGGAGGTGATGCAGTTCCT

GAACCGGAACCAACGTCTGCAGCCCTCTGCCCAAGCTCTCATCTACTTC

CGGGATTCCAGCTTCCTCAGCTCTGTGCCAGATGCCTGGAAATCTGACT

TTGTTTCTGAGTCTGAAGAGGCCGCATGTCGGATCTCAGAACTGAAGAG

CTACCTAAGCAGACAGAAAGGGATAACCTGCCGCAGATACCCCTGTGAG

TGGGGGGGTGTGGCAGCTGGCCGGCCCTATGTTGGCGGGCTGGAGGAGT

TTGGGCAGTTGGTTCTGCAGGATGTATGGAATATGATCCAGAAGCTCTA

CCTGCAGCCTGGGGCCCTGCTGGAGCAGCCAGTGTCCATCCCAGACGAT

GACTTGGTCCAGGCCACCTTCCAGCAGCTGCAGAAGCCACCGAGTCCTG

CCCGGCCACGCCTTCTTCAGGACACAGTGCAACAGCTGATGCTGCCCCA

CGGAAGGCTGAGCCTGGTGACGGGGCAGTCAGGACAGGGCAAGACAGCC

TTCCTGGCATCTCTTGTGTCAGCCCTGCAGGCTCCTGATGGGGCCAAGG

TGGCACCATTAGTCTTCTTCCACTTTTCTGGGGCTCGTCCTGACCAGGG

TCTTGCCCTCACTCTGCTCAGACGCCTCTGTACCTATCTGCGTGGCCAA

CTAAAAGAGCCAGGTGCCCTCCCCAGCACCTACCGAAGCCTGGTGTGGG

FIG.1E

AGCTGCAGCAGAGGCTGCTGCCCAAGTCTGCTGAGTCCCTGCATCCTGG

CCAGACCCAGGTCCTGATCATCGATGGGGCTGATAGGTTAGTGGACCAG

AATGGGCAGCTGATTTCAGACTGGATCCCAAAGAAGCTTCCCCGGTGTG

TACACCTGGTGCTGAGTGTGTCTAGTGATGCAGGCCTAGGGGAGACCCT

TGAGCAGAGCCAGGGTGCCCACGTGCTGGCCTTGGGGCCTCTGGAGGCC

TCTGCTCGGGCCCGGCTGGTGAGAGAGGAGCTGGCCCTGTACGGGAAGC

GGCTGGAGGAGTCACCATTTAACAACCAGATGCGACTGCTGCTGGTGAA

GCGGGAATCAGGCCGGCCGCTCTACCTGCGCTTGGTCACCGATCACCTG

AGGCTCTTCACGCTGTATGAGCAGGTGTCTGAGAGACTCCGGACCCTGC

CTGCCACTGTCCCCCTGCTGCTGCAGCACATCCTGAGCACACTGGAGAA

GGAGCACGGGCCTGATGTCCTTCCCCAGGCCTTGACTGCCCTAGAAGTC

ACACGGAGTGGTTTGACTGTGGACCAGCTGCACGGAGTGCTGAGTGTGT

GGCGGACACTACCGAAGGGGACTAAGAGCTGGGAAGAAGCAGTGGCTGC

TGGTAACAGTGGAGACCCCTACCCCATGGGCCCGTTTGCCTGCCTCGTC

CAGAGTCTGCGCAGTTTGCTAGGGGAGGGCCCTCTGGAGCGCCCTGGTG

CCCGGCTGTGCCTCCCTGATGGGCCCCTGAGAACAGCAGCTAAACGTTG

CTATGGGAAGAGGCCAGGGCTAGAGGACACGGCACACATCCTCATTGCA

GCTCAGCTCTGGAAGACATGTGACGCTGATGCCTCAGGCACCTTCCGAA

GTTGCCCTCCTGAGGCTCTGGGAGACCTGCCTTACCACCTGCTCCAGAG

FIG. 1F

CGGGAACCGTGGACTTCTTTCGAAGTTCCTTACCAACCTCCATGTGGTG

GCTGCACACTTGGAATTGGGTCTGGTCTCTCGGCTCTTGGAGGCCCATG

CCCTCTATGCTTCTTCAGTCCCCAAAGAGGAACAAAAGCTCCCCGAGGC

TGACGTTGCAGTGTTTCGCACCTTCCTGAGGCAGCAGGCTTCAATCCTC

AGCCAGTACCCCCGGCTCCTGCCCCAGCAGGCAGCCAACCAGCCCCTGG

ACTCACCTCTTTGCCACCAAGCCTCGCTGCTCTCCCGGAGATGGCACCT

CCAACACACACTACGATGGCTTAATAAACCCCGGACCATGAAAAATCAG

CAAAGCTCCAGCCTGTCTCTGGCAGTTTCCTCATCCCCTACTGCTGTGG

CCTTCTCCACCAATGGGCAAAGAGCAGCTGTGGGCACTGCCAATGGGAC

AGTTTACCTGTTGGACCTGAGAACTTGGCAGGAGGAGAAGTCTGTGGTG

AGTGGCTGTGATGGAATCTCTGCTTGTTTGTTCCTCTCCGATGATACAC

TCTTTCTTACTGCCTTCGACGGGCTCCTGGAGCTCTGGGACCTGCAGCA

TGGTTGTCGGGTGCTGCAGACTAAGGCTCACCAGTACCAAATCACTGGC

TGCTGCCTGAGCCCAGACTGCCGGCTGCTAGCCACCGTGTGCTTGGGAG

GATGCCTAAAGCTGTGGGACACAGTCCGTGGGCAGCTGGCCTTCCAGCA

CACCTACCCCAAGTCCCTGAACTGTGTTGCCTTCCACCCAGAGGGGCAG

GTAATAGCCACAGGCAGCTGGGCTGGCAGCATCAGCTTCTTCCAGGTGG

ATGGGCTCAAAGTCACCAAGGACCTGGGGGCACCCGGAGCCTCTATCCG

TACCTTGGCCTTCAATGTGCCTGGGGGGGTTGTGGCTGTGGGCCGGCTG

FIG.1G

GACAGTATGGTGGAGCTGTGGGCCTGGCGAGAAGGGGCACGGCTGGCTG
CCTTCCCTGCCCACCATGGCTTTGTTGCTGCTGCGCTTTTCCTGCATGC
GGGTTGCCAGTTACTGACGGCTGGAGAGGATGGCAAGGTTCAGGTGTGG
TCAGGGTCTCTGGGTCGGCCCCGTGGGCACCTGGGTTCCCTTTCTCTCT
CTCCTGCCCTCTCTGTGGCACTCAGCCCAGATGGTGATCGGGTGGCTGT
TGGATATCGAGCGGATGGCATTAGGATCTACAAAATCTCTTCAGGTTCC
CAGGGGGCTCAGGGTCAGGCACTGGATGTGGCAGTGTCCGCCCTGGCCT
GGCTAAGCCCCAAGGTATTGGTGAGTGGTGCAGAAGATGGGTCCTTGCA
GGGCTGGGCACTCAAGGAATGCTCCCTTCAGTCCCTCTGGCTCCTGTCC
AGATTCCAGAAGCCTGTGCTAGGACTGGCCACTTCCCAGGAGCTCTTGG
CTTCTGCCTCAGAGGATTTCACAGTGCAGCTGTGGCCAAGGCAGCTGCT
GACGCGGCCACACAAGGCAGAAGACTTTCCCTGTGGCACTGAGCTGCGG
GGACATGAGGGCCCTGTGAGCTGCTGTAGTTTCAGCACTGATGGAGGCA
GCCTGGCCACCGGGGGCCGGGATCGGAGTCTCCTCTGCTGGGACGTGAG
GACACCCAAAACCCCTGTTTTGATCCACTCCTTCCCTGCCTGTCACCGT
GACTGGGTCACTGGCTGTGCCTGGACCAAAGATAACCTACTGATATCCT
GCTCCAGTGATGGCTCTGTGGGGCTCTGGGACCCAGAGTCAGGACAGCG
GCTTGGTCAGTTCCTGGGTCATCAGAGTGCTGTGAGCGCTGTGGCAGCT
GTGGAGGAGCACGTGGTGTCTGTGAGCCGGGATGGGACCTTGAAAGTGT

FIG.1H

GGGACCATCAAGGCGTGGAGCTGACCAGCATCCCTGCTCACTCAGGACC

CATTAGCCACTGTGCAGCTGCCATGGAGCCCCGTGCAGCTGGACAGCCT

GGGTCAGAGCTTCTGGTGGTAACCGTCGGGCTAGATGGGGCCACACGGT

TATGGCATCCACTCTTGGTGTGCCAAACCCACACCCTCCTGGGACACAG

CGGCCCAGTCCGTGCTGCTGCTGTTTCAGAAACCTCAGGCCTCATGCTG

ACCGCCTCTGAGGATGGTTCTGTACGGCTCTGGCAGGTTCCTAAGGAAG

CAGATGACACATGTATACCAAGGAGTTCTGCAGCCGTCACTGCTGTGGC

TTGGGCACCAGATGGTTCCATGGCAGTATCTGGAAATCAAGCTGGGGAA

CTAATCTTGTGGCAGGAAGCTAAGGCTGTGGCCACAGCACAGGCTCCAG

GCCACATTGGTGCTCTGATCTGGTCCTCGGCACACACCTTTTTTGTCCT

CAGTGCTGATGAGAAAATCAGCGAGTGGCAAGTGAAACTGCGGAAGGGT

TCGGCACCCGGAAATTTGAGTCTTCACCTGAACCGAATTCTACAGGAGG

ACTTAGGGGTGCTGACAAGTCTGGATTGGGCTCCTGATGGTCACTTTCT

CATCTTGGCCAAAGCAGATTTGAAGTTACTTTGCATGAAGCCAGGGGAT

GCTCCATCTGAAATCTGGAGCAGCTATACAGAAAATCCTATGATATTGT

CCACCCACAAGGAGTATGGCATATTTGTCCTGCAGCCCAAGGATCCTGG

AGTTCTTTCTTTCTTGAGGCAAAAGGAATCAGGAGAGTTTGAAGAGAGG

CTGAACTTTGATATAAACTTAGAGAATCCTAGTAGGACCCTAATATCGA

TAACTCAAGCCAAACCTGAATCTGAGTCCTCATTTTTGTGTGCCAGCTC

FIG. 1I

TGATGGGATCCTATGGAACCTGGCCAAATGCAGCCCAGAAGGAGAATGG

ACCACAGGTAACATGTGGCAGAAAAAAGCAAACACTCCAGAAACCCAAA

CTCCAGGGACAGACCCATCTACCTGCAGGGAATCTGATGCCAGCATGGA

TAGTGATGCCAGCATGGATAGTGAGCCAACACCACATCTAAAGACACGG

CAGCGTAGAAAGATTCACTCGGGCTCTGTCACAGCCCTCCATGTGCTAC

CTGAGTTGCTGGTGACAGCTTCGAAGGACAGAGATGTTAAGCTATGGGA

GAGACCCAGTATGCAGCTGCTGGGCCTGTTCCGATGCGAAGGGTCAGTG

AGCTGCCTGGAACCTTGGCTGGGCGCTAACTCCACCCTGCAGCTTGCCG

TGGGAGACGTGCAGGGCAATGTGTACTTTCTGAATTGGGAA

FIG.2A

ATGGAGAAGCTCTGTGGGCATGTGCCTGGCCATTCAGACATCCTCTCCT
TGAAGAACCGGTGCCTGACCATGCTCCCTGACCTCCAGCCCCTGGAGAA
AATACATGGACATAGATCTGTCCACTCAGACATCCTTTCCTTGGAGAAC
CAGTGTCTGACCATGCTCTCTGACCTCCAGCCCACGGAGAGAATAGATG
GGCATATATCTGTCCACCCAGACATCCTCTCCTTGGAGAATCGGTGCCT
GACCATGCTCCCTGACCTCCAGCCTCTGGAGAAGCTATGTGGACATATG
TCTAGTCATCCAGACGTCCTTTCTTTGGAAAACCAATGTCTAGCTACTC
TCCCCACTGTAAAGAGCACTGCATTGACCAGCCCCTTGCTCCAGGGTCT
TCACATATCTCATACGGCACAAGCTGATCTGCATAGCCTGAAAACTAGC
AACTGCCTGCTCCCTGAGCTTCCTACCAAGAAGACTCCATGTTTCTCTG
AGGAACTAGACCTTCCACCTGGACCCAGGGCCCTGAAATCCATGTCTGC
TACAGCTCAAGTCCAGGAAGTAGCCTTGGGTCAATGGTGTGTCTCCAAA
GAAAAGGAATTTCAAGAAGAAGAAAGCACAGAAGTCCCRATGCCTTTGT
ACAGTCTAAGCTTGGAAGAAGAAGAAGTGGAGGCACCGGTCTTAAAACT
CACATCTGGAGACTCTGGCTTTCATCCTGAAACCACTGACCAGGTCCTT
CAGGAGAAGAAGATGGCTCTCTTGACCTTACTCTGCTCTGCTCTGGCCT
CAAATGTGAATGTGAAAGATGCATCTGACCTTACCCGGGCATCCATCCT
TGAAGTCTGTAGTGCCCTGGCCTCCTTGGAACCGGAGTTCATCCTTAAG
GCATCTTTGTATGCTCGGCAGCAACTTAACCTCCGGGACATCGCCAATA

FIG.2B

CAGTTCTGGCTGTGGCTGCCCTCTTGCCAGCCTGCCGCCCCCATGTACG

ACGGTATTACTCCGCCATTGTTCACCTGCCTTCAGACTGGATCCAGGTA

GCCGAGTTCTACCAGAGCCTGGCAGAAGGGGATGAGAAGAAGTTGGTGT

CCCTGCCTGCCTGTCTCCGAGCTGCCATGACCGACAAATTTGCCGAGTT

TGATGAGTACCAGCTAGCTAAGTACAACCCACGGAAACATCGGTCCAAG

AGGCGGTCCCGCCAGCCACCCCGCCCTCAAAAGACAGAACGTCCATTTT

CAGAGAGAGGGAAATGTTTTCCAAAGAGCCTTTGGCCCCTTAAAAATGA

ACAGATTACGTTTGAAGCAGCTTATAATGCAATGCCAGAGAAAAACAGG

CTACCACGGTTCACTCTGAAGAAGTTGGTAGAGTATCTACATATCCACA

AGCCTGCTCAGCACGTCCAGGCCCTGCTGGGCTACAGGTACCCAGCCAC

CCTAGAGCTCTTTTCTCGGAGTCACCTCCCTGGGCCGTGGGAGTCTAGC

AGAGCTGGTCAGCGGATGAAGCTCCGAAGGCCAGAGACCTGGGAGCGGG

AGCTGAGTTTACGGGGAAACAAAGCTTCTGTGTGGGAGGAGCTCATAGA

CAATGGGAAACTGCCCTTCATGGCCATGCTCCGGAACCTGTGTAACCTG

CTGCGGACTGGGATCAGTGCCCGCCACCATGAACTCGTTCTCCAGAGAC

TCCAGCATGAGAAATCTGTGGTTCACAGTCGGCAGTTTCCATTCAGATT

CCTTAATGCTCATGACTCTATCGATAAACTTGAGGCTCAGCTCAGAAGC

AAAGCATCACCCTTCCCTTCCAATACAACATTGATGAAACGGATAATGA

TTAGAAACTCAAAAAAAAATAGGAGGCCTGCCAGTCGGAAGCACCTGTG

FIG.2C

CACCCTGACGCGCCGGCAGCTTCGGGCAGCAATGACTATACCTGTGATG
TATGAGCAGCTCAAGCGGGAGAAACTGAGGCTGCACAAGGCCAGACAAT
GGAACTGTGATGTTGAGTTGCTGGAGCGCTATCGCCAGGCCCTGGAAAC
AGCTGTGAACCTCTCAGTAAAGCACAACCTATCCCCGATGCCTGGCCGA
ACCCTCTTGGTCTATCTCACAGATGCAAATGCCGACAGGCTCTGTCCCA
AGAGTCACTCACAAGGGCCTCCCCTGAACTATGTGCTGCTGCTGATCGG
AATGATGGTGGCTCGAGCCGAGCAAGTGACTGTTTGCTTGTGTGGGGGA
GGATTTGTGAAGACACCGGTACTTACAGCCGATGAAGGCATCCTGAAGA
CTGCCATCAAACTTCAGGCTCAAGTCCAGGAGTTAGAAGGCAATGATGA
GTGGCCCCTGGACACTTTTGGGAAGTATCTGCTGTCTCTGGCTGTCCAA
AGGACCCCCATTGACAGGGTCATCCTGTTTGGTCAAAGGATGGATACCG
AGCTCCTGAAAGTAGCCAAACAGATTATCTGGCAGCATGTGAATTCCAA
GTGCCTCTTTGTTGGTGTCCTCCTACAGAAAACACAGTACATATCACCA
AATTTGAATCCCAACGATGTGACGCTCTCAGGCTGCACTGACGGGATCC
TGAAATTCATTGCCGAACATGGAGCCTCTCGTCTCCTGGAACATGTGGG
ACAACTAGATAAACTATTCAAGATCCCCCCACCCCCAGGAAAGACACAG
GCACCGTCTCTCCGGCCGCTGGAGGAGAACATCCCTGGTCCCTTGGGTC
CTATTTCCCAGCATGGATGGCGCAATATCCGGCTTTTCATTTCATCCAC
TTTCCGTGACATGCATGGGGAGCGAGATTTGCTGATGAGATCTGTTCTG

FIG.2D

CCCGCACTGCAGGCCAGAGTGTTCCCCCACCGCATCAGTCTTCACGCCA

TTGACCTGCGCTGGGGTATCACAGAGGAAGAGACCCGCAGGAACAGACA

ACTGGAAGTGTGCCTTGGGGAGGTGGAGAACTCACAGCTGTTCGTGGGG

ATTCTGGGCTCCCGCTATGGCTACATTCCCCCCAGCTATGATCTTCCTG

ATCATCCCCACTTTCACTGGACCCATGAGTACCCTTCAGGGCGATCCGT

GACAGAGATGGAGGTGATGCAATTCCTGAACCGTGGCCAACGCTCGCAG

CCTTCGGCCCAAGCTCTCATCTACTTCCGAGATCCTGATTTCCTTAGCT

CTGTGCCAGATGCCTGGAAACCTGACTTTATATCTGAGTCAGAAGAAGC

TGCACATCGGGTCTCAGAGCTGAAGAGATATCTACACGAACAGAAAGAG

GTTACCTGTCGCAGCTACTCCTGTGAATGGGGAGGTGTAGCGGCTGGCC

GGCCCTATACTGGGGGCCTGGAGGAGTTTGGACAGTTGGTTCTCCAGGA

TGTGTGGAGCATGATCCAGAAGCAGCACCTGCAGCCTGGGGCCCAGTTG

GAGCAGCCAACATCCATCTCAGAAGACGATTTGATCCAGACCAGCTTTC

AGCAGCTGAAGACCCCAACGAGTCCGGCACGGCCACGCCTTCTTCAGGA

TACAGTGCAGCAGCTGTTGCTGCCCCATGGGAGGCTGAGCCTAGTGACT

GGGCAGGCAGGACAGGGAAAGACTGCCTTTCTGGCATCCCTTGTGTCTG

CCCTGAAGGTCCCTGACCAGCCCAATGAGCCCCCGTTCGTTTTCTTCCA

CTTTGCAGCAGCCCGCCCTGACCAGTGTCTTGCTCTCAACCTCCTCAGA

CGCCTCTGTACCCATCTGCGTCAAAAACTGGGAGAGCTGAGTGCCCTCC

FIG.2E

CCAGCACTTACAGAGGCCTGGTGTGGGAACTGCAGCAGAAGTTGCTCCT
CAAATTCGCTCAGTCGCTGCAGCCTGCTCAGACTTTGGTCCTTATCATC
GATGGGGCAGATAAGTTGGTGGATCGTAATGGGCAGCTGATTTCAGACT
GGATCCCCAAGTCTCTTCCGCGGCGAGTACACCTGGTGCTGAGTGTGTC
CAGTGACTCAGGCCTGGGTGAGACCCTTCAGCAAAGTCAGGGTGCTTAT
GTGGTGGCCTTGGGCTCTTTGGTCCCATCTTCAAGGGCTCAGCTTGTGA
GAGAAGAGCTAGCACTGTATGGGAAACGACTGGAGGAGTCACCTTTTAA
CAACCAGATGCGGCTGCTGCTGGCAAAGCAGGGTTCAAGCCTGCCATTG
TACCTGCACCTTGTCACTGACTACCTGAGGCTCTTCACACTGTATGAAC
AGGTGTCTGAGAGACTTCGAACCCTGCCCGCCACTCTCCCACTGCTCTT
GCAGCACATCCTGAGCACCTTGGAGCAAGAACATGGCCATGATGTCCTT
CCTCAGGCTTTGACTGCCCTTGAGGTCACACGAAGTGGTCTGACTGTGG
ACCAGCTACATGCAATCCTGAGCACATGGCTGATCTTGCCCAAGGAGAC
TAAGAGCTGGGAAGAAGTGCTGGCTGCCAGTCACAGTGGAAACCCTTTC
CCCTTGTGTCCATTTGCCTACCTTGTCCAGAGTCTACGCAGTTTACTAG
GGGAGGGCCCAGTGGAGCGCCCTGGTGCCCGTCTCTGCCTCTCTGATGG
GCCCCTGAGGACAACAATTAAACGTCGCTATGGAAAAGGCTGGGGCTA
GAGAAGACTGCGCATGTCCTCATTGCAGCTCACCTCTGGAAGACGTGTG
ATCCTGATGCCTCGGGCACCTTCCGAAGTTGCCCTCCTGAGGCTCTGAA

FIG.2F

AGATTTACCTTACCACCTGCTCCAGAGCGGGAACCATGGTCTCCTTGCC
GAGTTTCTTACCAATCTCCATGTGGTTGCTGCATATCTGGAAGTGGGTC
TAGTCCCCGACCTCTTGGAGGCTCATGTGCTCTATGCTTCTTCAAAGCC
TGAAGCCAACCAGAAGCTCCCAGCGGCAGATGTTGCTGTTTTCCATACC
TTCCTGAGACAACAGGCTTCACTCCTTACCCAGTATCCTTTGCTCCTGC
TCCAGCAGGCAGCTAGCCAGCCTGAAGAGTCACCTGTTTGCTGCCAGGC
CCCCCTGCTCACCCAGCGATGGCACGACCAGTTCACACTGAAATGGATT
AATAAACCCCAGACCCTGAAGGGTCAGCAAAGCTTGTCTCTGACAATGT
CCTCATCCCCAACTGCTGTGGCCTTCTCCCCGAATGGGCAAAGAGCAGC
TGTGGGGACCGCCAGTGGGACAATTTACCTGTTGAACTTGAAAACCTGG
CAGGAGGAGAAGGCTGTGGTGAGTGGCTGTGACGGGATTTCCTCTTTTG
CATTCCTTTCGGACACTGCCCTTTTCCTTACTACCTTCGACGGGCACCT
AGAGCTTTGGGACCTGCAACATGGTTGTTGGGTGTTTCAGACCAAGGCC
CACCAGTACCAAATCACTGGCTGCTGCCTGAGCCCAGACCGCCGCCTGC
TGGCCACTGTGTGTTTGGGAGGATACCTAAAGCTGTGGGACACAGTCCG
AGGACAGCTGGCTTTTCAGTACACCCATCCAAAGTCTCTCAACTGCGTT
GCCTTCCACCCAGAGGGGCAGGTGGTAGCCACAGGCAGCTGGGCTGGCA
GCATTACCTTCTTCCAGGCAGATGGACTCAAAGTCACCAAGGAACTAGG
GGCCCCCGGACCCTCTGTCTGTAGTTTGGCATTCAACAAACCTGGGAAG

FIG.2G

ATTGTGGCTGTGGGCCGGATAGATGGGACAGTGGAGCTGTGGGCCTGGC
AAGAGGGTGCCCGGCTGGCGGCCTTCCCTGCACAGTGTGGCTGTGTCTC
TGCTGTTCTTTTCTTGCATGCTGGAGACCGGTTCCTGACTGCTGGAGAA
GATGGCAAGGCTCAGTTATGGTCAGGATTTCTTGGCCGGCCCAGGGGTT
GCCTGGGCTCTCTTCCTCTTTCTCCTGCACTCTCGGTGGCTCTCAACCC
AGACGGTGACCAGGTGGCTGTTGGGTACCGAGAAGATGGCATTAACATC
TACAAGATTTCTTCAGGTTCCCAGGGGCCTCAGCATCAAGAGCTAAATG
TGGCGGTGTCTGCACTGGTGTGGCTGAGCCCTAGTGTTTTGGTGAGTGG
TGCAGAAGATGGATCCCTGCATGGTTGGATGTTCAAGGGAGACTCCCTT
CATTCCCTGTGGCTGTTGTCGAGATACCAGAAGCCTGTGCTGGGACTGG
CTGCCTCCCGGGAACTCATGGCTGCTGCCTCAGAGGACTTCACTGTGAG
ACTGTGGCCCAGACAGCTGCTGACACAGCCACATGTGCATGCGGTAGAG
TTGCCCTGTTGTGCTGAACTCCGGGGACACGAGGGGCCAGTGTGCTGCT
GTAGCTTCAGCCCTGATGGAGGCATCTTGGCCACAGCTGGCAGGGATCG
GAATCTCCTTTGCTGGGACATGAAGATAGCCCAAGCCCCTCTCCTGATT
CACACTTTCTCGTCCTGTCATCGTGACTGGATCACTGGCTGTGCGTGGA
CCAAAGACAACATCCTGGTCTCCTGCTCGAGTGATGGCTCTGTGGGACT
CTGGAACCCAGAGGCAGGGCAGCAACTTGGCCAGTTCTCAGGCCACCAG
AGTGCCGTGAGCGCCGTGGTTGCTGTGGAGGAACACATTGTATCTGTGA

FIG.2H

GCCGAGATGGGACCTTGAAAGTGTGGGACCATCAGGGTGTGGAGCTGAC
CAGCATCCCTGCCCATTCCGGACCCATCAGCCAGTGTGCAGCTGCTCTG
GAGCCCCGCCCAGGGGGACAGCCTGGATCAGAGCTTCTGGTGGTGACTG
TTGGACTAGATGGGGCCACAAAGTTGTGGCATCCCCTGTTGGTGTGCCA
AATACGTACTCTCCAGGGACACAGTGGCCCAGTCACAGCAGCTGCTGCT
TCAGAGGCCTCAGGCCTCCTGCTGACCTCAGATGATAGCTCTGTACAGC
TCTGGCAGATACCAAAGGAAGCAGATGATTCATACAAACCTAGGAGTTC
TGTGGCCATCACTGCTGTGGCATGGGCACCGGATGGTTCTATGGTGGTG
TCCGGAAATGAAGCCGGGGAACTGACACTGTGGCAGCAAGCCAAGGCTG
TGGCTACCGCACAGGCTCCAGGCCGCGTCAGTCACCTGATCTGGTACTC
GGCAAATTCATTCTTCGTTCTCAGTGCTAATGAAAACGTCAGCGAGTGG
CAAGTGGGACTGAGGAAAGGTTCAACGTCCACCAGTTCCAGTCTTCATC
TGAAGAGAGTTCTGCAGGAGGACTGGGGAGTCTTGACAGGTCTGGGTCT
GGCCCCTGATGGCCAGTCTCTCATCTTGATGAAAGAGGATGTGGAATTA
CTAGAGATGAAGCCTGGGTCTATTCCATCTTCTATCTGCAGGAGGTATG
GAGTACATTCTTCAATACTGTGCACCAGCAAGGAGTACGGCTTGTTCTA
CCTGCAGCAGGGGGACTCCGGATTACTTTCTATATTGGAGCAAAAGGAG
TCAGGGGAGTTTGAAGAGATCCTGGACTTCAATCTGAACTTAAATAATC
CTAATGGGTCCCCAGTATCAATCACTCAGGCCAAACCTGAGTCTGAATC

FIG.2I

ATCCCTTTTGTGCGCCACCTCTGATGGGATGCTGTGGAACTTATCTGAA
TGTACCTCAGAGGGAGAATGGATCGTAGATAACATTTGGCAGAAAAAAG
CAAAAAAACCTAAAACTCAGACTCTGGAGACAGAGTTGTCCCCGCACTC
AGAGTTGGATTTTTCCATTGATTGCTGGATTGATCCCACAAATTTAAAG
GCACAGCAGTGTAAAAAGATCCACTTGGGCTCTGTCACAGCCCTCCATG
TGCTTCCGGGATTGCTGGTGACAGCTTCGAAGGACAGAGATGTTAAGCT
GTGGGAGAGACCCAGTATGCAGCTGCTGGGCTTGTTCCGATGTGAAGGG
CCAGTGAGCTGTCTGGAACCTTGGATGGAGCCCAGCTCTCCCCTGCAGC
TTGCTGTGGGAGACACACAAGGAAACTTGTATTTTCTATCTTGGGAA

FIG.3A

MEKLHGHVSAHPDILSLENRCLAMLPDLQPLEKLHQHVSTHSDILSLKN
QCLATLPDLKTMEKPHGYVSAHPDILSLENQCLATLSDLKTMEKPHGHV
SAHPDILSLENRCLATLPSLKSTVSASPLFQSLQISHMTQADLYRVNNS
NCLLSEPPSWRAQHFSKGLDLSTCPIALKSISATETAQEATLGRWFDSE
EKKGAETQMPSYSLSLGEEEEVEDLAVKLTSGDSESHPEPTDHVLQEKK
MALLSLLCSTLVSEVNMNNTSDPTLAAIFEICRELALLEPEFILKASLY
ARQQLNVRNVANNILAIAAFLPACRPHLRRYFCAIVQLPSDWIQVAELY
QSLAEGDKNKLVPLPACLRTAMTDKFAQFDEYQLAKYNPRKHRAKRHPR
RPPRSPGMEPPFSHRCFPRYIGFLREEQRKFEKAGDTVSEKKNPPRFTL
KKLVQRLHIHKPAQHVQALLGYRYPSNLQLFSRSRLPGPWDSSRAGKRM
KLSRPETWERELSLRGNKASVWEELIENGKLPFMAMLRNLCNLLRVGIS
SRHHELILQRLQHGKSVIHSRQFPFRFLNAHDAIDALEAQLRNQALPFP
SNITLMRRILTRNEKNRPRRRFLCHLSRQQLRMAMRIPVLYEQLKREKL
RVHKARQWKYDGEMLNRYRQALETAVNLSVKHSLPLLPGRTVLVYLTDA
NADRLCPKSNPQGPPLNYALLLIGMMITRAEQVDVVLCGGDTLKTAVLK
AEEGILKTAIKLQAQVQEFDENDGWSLNTFGKYLLSLAGQRVPVDRVIL
LGQSMDDGMINVAKQLYWQRVNSKCLFVGILLRRVQYLSTDLNPNDVTL
SGCTDAILKFIAEHGASHLLEHVGQMDKIFKIPPPPGKTGVQSLRPLEE
DTPSPLAPVSQQGWRSIRLFISSTFRDMHGERDLLLRSVLPALQARAAP

FIG.3B

HRISLHGIDLRWGVTEEETRRNRQLEVCLGEVENAQLFVGILGSRYGYI
PPSYNLPDHPHFHWAQQYPSGRSVTEMEVMQFLNRNQRLQPSAQALIYF
RDSSFLSSVPDAWKSDFVSESEEAAXRISELKSYLSRQKGITCRRYPCE
WGGVAAGRPYVGGLEEFGQLVLQDVWNMIQKLYLQPGALLEQPVSIPDD
DLVQATFQQLQKPPSPARPRLLQDTVQXLMLPHGRLSLVTGQSGQGKTA
FLASLVSALQAPDGAKVAXLVFFHFSGARPDQGLALTLLRRLCTYLRGQ
LKEPGALPSTYRSLVWELQQRLLPKSAESLHPGQTQVLIIDGADRLVDQ
NGQLISDWIPKKLPRCVHLVLSVSSDAGLGETLEQSQGAHVLALGPLEA
SARARLVREELALYGKRLEESPFNNQMRLLLVKRESGRPLYLRLVTDHL
RLFTLYEQVSERLRTLPATVPLLLQHILSTLEKEHGPDVLPQALTALEV
TRSGLTVDQLHGVLSVWRTLPKGTKSWEEAVAAGNSGDPYPMGPFACLV
QSLRSLLGEGPLERPGARLCLPDGPLRTAAKRCYGKRPGLEDTAHILIA
AQLWKTCDADASGTFRSCPPEALGDLPYHLLQSGNRGLLSKFLTNLHVV
AAHLELGLVSRLLEAHALYASSVPKEEQKLPEADVAVFRTFLRQQASIL
SQYPRLLPQQAANQPLDSPLCHQASLLSRRWHLQHTLRWLNKPRTMKNQ
QSSSLSLAVSSSPTAVAFSTNGQRAAVGTANGTVYLLDLRTWQEEKSVV
SGCDGISACLFLSDDTLFLTAFDGLLELWDLQHGCRVLQTKAHQYQITG
CCLSPDCRLLATVCLGGCLKLWDTVRGQLAFQHTYPKSLNCVAFHPEGQ
VIATGSWAGSISFFQVDGLKVTKDLGAPGASIRTLAFNVPGGVVAVGRL

FIG.3C

DSMVELWAWREGARLAAFPAHHGFVAAALFLHAGCQLLTAGEDGKVQVW
SGSLGRPRGHLGSLSLSPALSVALSPDGDRVAVGYRADGIRIYKISSGS
QGAQGQALDVAVSALAWLSPKVLVSGAEDGSLQGWALKECSLQSLWLLS
RFQKPVLGLATSQELLASASEDFTVQLWPRQLLTRPHKAEDFPCGTELR
GHEGPVSCCSFSTDGGSLATGGRDRSLLCWDVRTPKTPVLIHSFPACHR
DWVTGCAWTKDNLLISCSSDGSVGLWDPESGQRLGQFLGHQSAVSAVAA
VEEHVVSVSRDGTLKVWDHQGVELTSIPAHSGPISHCAAAMEPRAAGQP
GSELLVVTVGLDGATRLWHPLLVCQTHTLLGHSGPVRAAAVSETSGLML
TASEDGSVRLWQVPKEADDTCIPRSSAAVTAVAWAPDGSMAVSGNQAGE
LILWQEAKAVATAQAPGHIGALIWSSAHTFFVLSADEKISEWQVKLRKG
SAPGNLSLHLNRILQEDLGVLTSLDWAPDGHFLILAKADLKLLCMKPGD
APSEIWSSYTENPMILSTHKEYGIFVLQPKDPGVLSFLRQKESGEFEER
LNFDINLENPSRTLISITQAKPESESSFLCASSDGILWNLAKCSPEGEW
TTGNMWQKKANTPETQTPGTDPSTCRESDASMDSDASMDSEPTPHLKTR
QRRKIHSGSVTALHVLPELLVTASKDRDVKLWERPSMQLLGLFRCEGSV
SCLEPWLGANSTLQLAVGDVQGNVYFLNWE

FIG.4A

MEKLCGHVPGHSDILSLKNRCLTMLPDLQPLEKIHGHRSVHSDILSLEN
QCLTMLSDLQPTERIDGHISVHPDILSLENRCLTMLPDLQPLEKLCGHM
SSHPDVLSLENQCLATLPTVKSTALTSPLLQGLHISHTAQADLHSLKTS
NCLLPELPTKKTPCFSEELDLPPGPRALKSMSATAQVQEVALGQWCVSK
EKEFQEEESTEVPMPLYSLSLEEEEVEAPVLKLTSGDSGFHPETTDQVL
QEKKMALLTLLCSALASNVNVKDASDLTRASILEVCSALASLEPEFILK
ASLYARQQLNLRDIANTVLAVAALLPACRPHVRRYYSAIVHLPSDWIQV
AEFYQSLAEGDEKKLVSLPACLRAAMTDKFAEFDEYQLAKYNPRKHRSK
RRSRQPPRPQKTERPFSERGKCFPKSLWPLKNEQITFEAAYNAMPEKNR
LPRFTLKKLVEYLHIHKPAQHVQALLGYRYPATLELFSRSHLPGPWESS
RAGQRMKLRRPETWERELSLRGNKASVWEELIDNGKLPFMAMLRNLCNL
LRTGISARHHELVLQRLQHEKSVVHSRQFPFRFLNAHDSIDKLEAQLRS
KASPFPSNTTLMKRIMIRNSKKNRRPASRKHLCTLTRRQLRAAMTIPVM
YEQLKREKLRLHKARQWNCDVELLERYRQALETAVNLSVKHNLSPMPGR
TLLVYLTDANADRLCPKSHSQGPPLNYVLLLIGMMVARAEQVTVCLCGG
GFVKTPVLTADEGILKTAIKLQAQVQELEGNDEWPLDTFGKYLLSLAVQ
RTPIDRVILFGQRMDTELLKVAKQIIWQHVNSKCLFVGVLLQKTQYISP
NLNPNDVTLSGCTDGILKFIAEHGASRLLEHVGQLDKLFKIPPPPGKTQ
APSLRPLEENIPGPLGPISQHGWRNIRLFISSTFRDMHGERDLLMRSVL

FIG.4B

PALQARVFPHRISLHAIDLRWGITEEETRRNRQLEVCLGEVENSQLFVG
ILGSRYGYIPPSYDLPDHPHFHWTHEYPSGRSVTEMEVMQFLNRGQRSQ
PSAQALIYFRDPDFLSSVPDAWKPDFISESEEAAHRVSELKRYLHEQKE
VTCRSYSCEWGGVAAGRPYTGGLEEFGQLVLQDVWSMIQKQHLQPGAQL
EQPTSISEDDLIQTSFQQLKTPTSPARPRLLQDTVQQLLLPHGRLSLVT
GQAGQGKTAFLASLVSALKVPDQPNEPPFVFFHFAAARPDQCLALNLLR
RLCTHLRQKLGELSALPSTYRGLVWELQQKLLLKFAQSLQPAQTLVLII
DGADKLVDRNGQLISDWIPKSLPRRVHLVLSVSSDSGLGETLQQSQGAY
VVALGSLVPSSRAQLVREELALYGKRLEESPFNNQMRLLLAKQGSSLPL
YLHLVTDYLRLFTLYEQVSERLRTLPATLPLLLQHILSTLEQEHGHDVL
PQALTALEVTRSGLTVDQLHAILSTWLILPKETKSWEEVLAASHSGNPF
PLCPFAYLVQSLRSLLGEGPVERPGARLCLSDGPLRTTIKRRYGKRLGL
EKTAHVLIAAHLWKTCDPDASGTFRSCPPEALKDLPYHLLQSGNHGLLA
EFLTNLHVVAAYLEVGLVPDLLEAHVLYASSKPEANQKLPAADVAVFHT
FLRQQASLLTQYPLLLLQQAASQPEESPVCCQAPLLTQRWHDQFTLKWI
NKPQTLKGQQSLSLTMSSSPTAVAFSPNGQRAAVGTASGTIYLLNLKTW
QEEKAVVSGCDGISSFAFLSDTALFLTTFDGHLELWDLQHGCWVFQTKA
HQYQITGCCLSPDRRLLATVCLGGYLKLWDTVRGQLAFQYTHPKSLNCV
AFHPEGQVVATGSWAGSITFFQADGLKVTKELGAPGPSVCSLAFNKPGK

FIG.4C

IVAVGRIDGTVELWAWQEGARLAAFPAQCGCVSAVLFLHAGDRFLTAGE
DGKAQLWSGFLGRPRGCLGSLPLSPALSVALNPDGDQVAVGYREDGINI
YKISSGSQGPQHQELNVAVSALVWLSPSVLVSGAEDGSLHGWMFKGDSL
HSLWLLSRYQKPVLGLAASRELMAAASEDFTVRLWPRQLLTQPHVHAVE
LPCCAELRGHEGPVCCCSFSPDGGILATAGRDRNLLCWDMKIAQAPLLI
HTFSSCHRDWITGCAWTKDNILVSCSSDGSVGLWNPEAGQQLGQFSGHQ
SAVSAVVAVEEHIVSVSRDGTLKVWDHQGVELTSIPAHSGPISQCAAAL
EPRPGGQPGSELLVVTVGLDGATKLWHPLLVCQIRTLQGHSGPVTAAAA
SEASGLLLTSDDSSVQLWQIPKEADDSYKPRSSVAITAVAWAPDGSMVV
SGNEAGELTLWQQAKAVATAQAPGRVSHLIWYSANSFFVLSANENVSEW
QVGLRKGSTSTSSSLHLKRVLQEDWGVLTGLGLAPDGQSLILMKEDVEL
LEMKPGSIPSSICRRYGVHSSILCTSKEYGLFYLQQGDSGLLSILEQKE
SGEFEEILDFNLNLNNPNGSPVSITQAKPESESSLLCATSDGMLWNLSE
CTSEGEWIVDNIWQKKAKKPKTQTLETELSPHSELDFSIDCWIDPTNLK
AQQCKKIHLGSVTALHVLPGLLVTASKDRDVKLWERPSMQLLGLFRCEG
PVSCLEPWMEPSSPLQLAVGDTQGNLYFLSWE

FIG.5A

CACGCGTCCGGGCAGCGCTGCGTCCTGCTGCGCACGTGGGAAGCCCTGG
CCCCGGCCACCCCCGCGATGCCGCGCGCTCCCCGCTGCCGAGCCGTGCG
CTCCCTGCTGCGCAGCCACTACCGCGAGGTGCTGCCGCTGGCCACGTTC
GTGCGGCGCCTGGGGCCCCAGGGCTGGCGGCTGGTGCAGCGCGGGGACC
CGGCGGCTTTCCGCGCGCTGGTGGCCCAGTGCCTGGTGTGCGTGCCCTG
GGACGCACGGCCGCCCCCCGCCGCCCCCTCCTTCCGCCAGGTGTCCTGC
CTGAAGGAGCTGGTGGCCCGAGTGCTGCAGAGGCTGTGCGAGCGCGGCG
CGAAGAACGTGCTGGCCTTCGGCTTCGCGCTGCTGGACGGGGCCCGCGG
GGGCCCCCCCGAGGCCTTCACCACCAGCGTGCGCAGCTACCTGCCCAAC
ACGGTGACCGACGCACTGCGGGGGAGCGGGGCGTGGGGGCTGCTGCTGC
GCCGCGTGGGCGACGACGTGCTGGTTCACCTGCTGGCACGCTGCGCGCT
CTTTGTGCTGGTGGCTCCCAGCTGCGCCTACCAGGTGTGCGGGCCGCCG
CTGTACCAGCTCGGCGCTGCCACTCAGGCCCGGCCCCCGCCACACGCTA
GTGGACCCCGAAGGCGTCTGGGATGCGAACGGGCCTGGAACCATAGCGT
CAGGGAGGCCGGGGTCCCCCTGGGCCTGCCAGCCCCGGGTGCGAGGAGG
CGCGGGGGCAGTGCCAGCCGAAGTCTGCCGTTGCCCAAGAGGCCCAGGC
GTGGCGCTGCCCCTGAGCCGGAGCGGACGCCCGTTGGGCAGGGGTCCTG
GGCCCACCCGGGCAGGACGCGTGGACCGAGTGACCGTGGTTTCTGTGTG
GTGTCACCTGCCAGACCCGCCGAAGAAGCCACCTCTTTGGAGGGTGCGC

FIG.5B

TCTCTGGCACGCGCCACTCCCACCCATCCGTGGGCCGCCAGCACCACGC
GGGCCCCCCATCCACATCGCGGCCACCACGTCCCTGGGACACGCCTTGT
CCCCCGGTGTACGCCGAGACCAAGCACTTCCTCTACTCCTCAGGCGACA
AGGAGCAGCTGCGGCCCTCCTTCCTACTCAGCTCTCTGAGGCCCAGCCT
GACTGGCGCTCGGAGGCTCGTGGAGACCATCTTTCTGGGTTCCAGGCCC
TGGATGCCAGGGACTCCCCGCAGGTTGCCCCGCCTGCCCCAGCGCTACT
GGCAAATGCGGCCCCTGTTTCTGGAGCTGCTTGGGAACCACGCGCAGTG
CCCCTACGGGGTGCTCCTCAAGACGCACTGCCCGCTGCGAGCTGCGGTC
ACCCCAGCAGCCGGTGTCTGTGCCCGGGAGAAGCCCCAGGGCTCTGTGG
CGGCCCCCGAGGAGGAGGACACAGACCCCCGTCGCCTGGTGCAGCTGCT
CCGCCAGCACAGCAGCCCCTGGCAGGTGTACGGCTTCGTGCGGGCCTGC
CTGCGCCGGCTGGTGCCCCCAGGCCTCTGGGGCTCCAGGCACAACGAAC
GCCGCTTCCTCAGGAACACCAAGAAGTTCATCTCCCTGGGGAAGCATGC
CAAGCTCTCGCTGCAGGAGCTGACGTGGAAGATGAGCGTGCGGGACTGC
GCTTGGCTGCGCAGGAGCCCAGGGGTTGGCTGTGTTCCGGCCGCAGAGC
ACCGTCTGCGTGAGGAGATCCTGGCCAAGTTCCTGCACTGGCTGATGAG
TGTGTACGTCGTCGAGCTGCTCAGGTCTTTCTTTTATGTCACGGAGACC
ACGTTTCAAAAGAACAGGCTCTTTTTCTACCGGAAGAGTGTCTGGAGCA
AGTTGCAAAGCATTGGAATCAGACAGCACTTGAAGAGGGTGCAGCTGCG

FIG.5C

GGAGCTGTCGGAAGCAGAGGTCAGGCAGCATCGGGAAGCCAGGCCCGCC
CTGCTGACGTCCAGACTCCGCTTCATCCCCAAGCCTGACGGGCTGCGGC
CGATTGTGAACATGGACTACGTCGTGGGAGCCAGAACGTTCCGCAGAGA
AAAGAGGGCCGAGCGTCTCACCTCGAGGGTGAAGGCACTGTTCAGCGTG
CTCAACTACGAGCGGGCGCGGCGCCCCGGCCTCCTGGGCGCCTCTGTGC
TGGGCCTGGACGATATCCACAGGGCCTGGCGCACCTTCGTGCTGCGTGT
GCGGGCCCAGGACCCGCCGCCTGAGCTGTACTTTGTCAAGGTGGATGTG
ACGGGCGCGTACGACACCATCCCCCAGGACAGGCTCACGGAGGTCATCG
CCAGCATCATCAAACCCCAGAACACGTACTGCGTGCGTCGGTATGCCGT
GGTCCAGAAGGCCGCCCATGGGCACGTCCGCAAGGCCTTCAAGAGCCAC
GTCTCTACCTTGACAGACCTCCAGCCGTACATGCGACAGTTCGTGGCTC
ACCTGCAGGAGACCAGCCCGCTGAGGGATGCCGTCGTCATCGAGCAGAG
CTCCTCCCTGAATGAGGCCAGCAGTGGCCTCTTCGACGTCTTCCTACGC
TTCATGTGCCACCACGCCGTGCGCATCAGGGGCAAGTCCTACGTCCAGT
GCCAGGGGATCCCGCAGGGCTCCATCCTCTCCACGCTGCTCTGCAGCCT
GTGCTACGGCGACATGGAGAACAAGCTGTTTGCGGGGATTCGGCGGGAC
GGGCTGCTCCTGCGTTTGGTGGATGATTTCTTGTTGGTGACACCTCACC
TCACCCACGCGAAAACCTTCCTCAGGACCCTGGTCCGAGGTGTCCCTGA
GTATGGCTGCGTGGTGAACTTGCGGAAGACAGTGGTGAACTTCCCTGTA

FIG.5D

GAAGACGAGGCCCTGGGTGGCACGGCTTTTGTTCAGATGCCGGCCCACG

GCCTAT

FIG.6A

HASGQRCVLLRTWEALAPATPAMPRAPRCRAVRSLLRSHYREVLPLATF
VRRLGPQGWRLVQRGDPAAFRALVAQCLVCVPWDARPPPAAPSFRQVSC
LKELVARVLQRLCERGAKNVLAFGFALLDGARGGPPEAFTTSVRSYLPN
TVTDALRGSGAWGLLLRRVGDDVLVHLLARCALFVLVAPSCAYQVCGPP
LYQLGAATQARPPPHASGPRRRLGCERAWNHSVREAGVPLGLPAPGARR
RGGSASRSLPLPKRPRRGAAPEPERTPVGQGSWAHPGRTRGPSDRGFCV
VSPARPAEEATSLEGALSGTRHSHPSVGRQHHAGPPSTSRPPRPWDTPC
PPVYAETKHFLYSSGDKEQLRPSFLLSSLRPSLTGARRLVETIFLGSRP
WMPGTPRRLPRLPQRYWQMRPLFLELLGNHAQCPYGVLLKTHCPLRAAV
TPAAGVCAREKPQGSVAAPEEEDTDPRRLVQLLRQHSSPWQVYGFVRAC
LRRLVPPGLWGSRHNERRFLRNTKKFISLGKHAKLSLQELTWKMSVRDC
AWLRRSPGVGCVPAAEHRLREEILAKFLHWLMSVYVVELLRSFFYVTET
TFQKNRLFFYRKSVWSKLQSIGIRQHLKRVQLRELSEAEVRQHREARPA
LLTSRLRFIPKPDGLRPIVNMDYVVGARTFRREKRAERLTSRVKALFSV
LNYERARRPGLLGASVLGLDDIHRAWRTFVLRVRAQDPPPELYFVKVDV
TGAYDTIPQDRLTEVIASIIKPQNTYCVRRYAVVQKAAHGHVRKAFKSH
VSTLTDLQPYMRQFVAHLQETSPLRDAVVIEQSSSLNEASSGLFDVFLR
FMCHHAVRIRGKSYVQCQGIPQGSILSTLLCSLCYGDMENKLFAGIRRD

FIG.6B

GLLLRLVDDFLLVTPHLTHAKTFLRTLVRGVPEYGCVVNLRKTVVNFPV

EDEALGGTAFVQMPAHGL

FIG. 7

TCCCCTGGTGCGGCCTGCTGCTGGATACCCGGACCCTGGAGGTGCAGAGCGACT
ACTCCAGCTATGCCCGGACCTCCATCAGAGCCAGTCTCACCTTCAACCGCGGCT
TCAAGGCTGGGAGGAACATGCGTCGCAAACTCTTTGGGGTCTTGCGGCTGAAGT
GTCACAGCCTGTTTCTGGATTTGCAGGTGAACAGCCTCCAGACGGTGTGCACCA
ACATCTACAAGATCCTCCTGCTGCAGGCGTACAGGTTTCACGCATGTGTGCTGC
AGCTCCCATTTCATCAGCAAGTTTGGAAGAACCCCACATTTTTCCTGCGCGTCA
TCTCTGACACGGCCTCCCTCTGCTACTCCATCCTGAAAGCCAAGAACGCAGGGA
TGTCGCTGGGGGCCAAGGGCGCCGCCGGCCCTCTGCCCTCCGAGGCCGTGCAGT
GGCTGTGCCACCAAGCATTCCTGCTCAAGCTGACTCGACACCGTGTCACCTACG
TGCCACTCCTGGGGTCACTCAGGACAGCCCAGACGCAGCTGAGTCGGAAGCTCC
CGGGGACGACGCTGACTGCCCTGGAGGCCGCAGCCAACCCGGCACTGCCCTCAG
ACTTCAAGACCATCCTGGACTGATGGCCACCCGCCCACAGCCAGGCCGAGAGCA
GACACCAGCAGCCCTGTCACGCCGGGCTCTACGTCCCAGGGAGGGAGGGGCGGC
CCACACCCAGGCCCGCACCGCTGGGAGTCTGAGGCCTGAGTGAGTGTTTGGCCG
AGGCCTGCATGTCCGGCTGAAGGCTGAGTGTCCGGCTGAGGCCTGAGCGAGTGT
CCAGCCAAGGGCTGAGTGTCCAGCACACCTGCCGTCTTCACTTCCCCACAGGCT
GGCGCTCGGCTCCACCCCAGGGCCAGCTTTTCCTCACCAGGAGCCCGGCTTCCA
CTCCCCACATAGGAATAGTCCATCCCCTGAT

FIG.8A

CCACGCGTCCGGGCAGCGCTGCGTCCTGCTGCGCACGTGGGAAGCCCTGGCCCC
GGCCACCCCCGCGATGCCGCGCGCTCCCCGCTGCCGAGCCGTGCGCTCCCTGCT
GCGCAGCCACTACCGCGAGGTGCTGCCGCTGGCCACGTTCGTGCGGCGCCTGGG
GCCCCAGGGCTGGCGGCTGGTGCAGCGCGGGGACCCGGCGGCTTTCCGCGCGCT
GGTGGCCCAGTGCCTGGTGTGCGTGCCCTGGGACGCACGGCCGCCCCCCGCCGC
CCCCTCCTTCCGCCAGGTGTCCTGCCTGAAGGAGCTGGTGGCCCGAGTGCTGCA
GAGGCTGTGCGAGCGCGGCGCGAAGAACGTGCTGGCCTTCGGCTTCGCGCTGCT
GGACGGGGCCCGCGGGGGCCCCCCCGAGGCCTTCACCACCAGCGTGCGCAGCTA
CCTGCCCAACACGGTGACCGACGCACTGCGGGGGAGCGGGGCGTGGGGGCTGCT
GCTGCGCCGCGTGGGCGACGACGTGCTGGTTCACCTGCTGGCACGCTGCGCGCT
CTTTGTGCTGGTGGCTCCCAGCTGCGCCTACCAGGTGTGCGGGCCGCCGCTGTA
CCAGCTCGGCGCTGCCACTCAGGCCCGGCCCCCGCCACACGCTAGTGGACCCCG
AAGGCGTCTGGGATGCGAACGGGCCTGGAACCATAGCGTCAGGGAGGCCGGGGT
CCCCCTGGGCCTGCCAGCCCCGGGTGCGAGGAGGCGCGGGGGCAGTGCCAGCCG
AAGTCTGCCGTTGCCCAAGAGGCCCAGGCGTGGCGCTGCCCCTGAGCCGGAGCG
GACGCCCGTTGGGCAGGGGTCCTGGGCCCACCCGGGCAGGACGCGTGGACCGAG
TGACCGTGGTTTCTGTGTGGTGTCACCTGCCAGACCCGCCGAAGAAGCCACCTC
TTTGGAGGGTGCGCTCTCTGGCACGCGCCACTCCCACCCATCCGTGGGCCGCCA
GCACCACGCGGGCCCCCCATCCACATCGCGGCCACCACGTCCCTGGGACACGCC
TTGTCCCCCGGTGTACGCCGAGACCAAGCACTTCCTCTACTCCTCAGGCGACAA

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FIG.8B

GGAGCAGCTGCGGCCCTCCTTCCTACTCAGCTCTCTGAGGCCCAGCCTGACTGG

CGCTCGGAGGCTCGTGGAGACCATCTTTCTGGGTTCCAGGCCCTGGATGCCAGG

GACTCCCCGCAGGTTGCCCCGCCTGCCCCAGCGCTACTGGCAAATGCGGCCCCT

GTTTCTGGAGCTGCTTGGGAACCACGCGCAGTGCCCCTACGGGGTGCTCCTCAA

GACGCACTGCCCGCTGCGAGCTGCGGTCACCCCAGCAGCCGGTGTCTGTGCCCG

GGAGAAGCCCCAGGGCTCTGTGGCGGCCCCCGAGGAGGAGGACACAGACCCCCG

TCGCCTGGTGCAGCTGCTCCGCCAGCACAGCAGCCCCTGGCAGGTGTACGGCTT

CGTGCGGGCCTGCCTGCGCCGGCTGGTGCCCCCAGGCCTCTGGGGCTCCAGGCA

CAACGAACGCCGCTTCCTCAGGAACACCAAGAAGTTCATCTCCCTGGGGAAGCA

TGCCAAGCTCTCGCTGCAGGAGCTGACGTGGAAGATGAGCGTGCGGGACTGCGC

TTGGCTGCGCAGGAGCCCAGGGGTTGGCTGTGTTCCGGCCGCAGAGCACCGTCT

GCGTGAGGAGATCCTGGCCAAGTTCCTGCACTGGCTGATGAGTGTGTACGTCGT

CGAGCTGCTCAGGTCTTTCTTTTATGTCACGGAGACCACGTTTCAAAAGAACAG

GCTCTTTTTCTACCGGAAGAGTGTCTGGAGCAAGTTGCAAAGCATTGGAATCAG

ACAGCACTTGAAGAGGGTGCAGCTGCGGGAGCTGTCGGAAGCAGAGGTCAGGCA

GCATCGGGAAGCCAGGCCCGCCCTGCTGACGTCCAGACTCCGCTTCATCCCCAA

GCCTGACGGGCTGCGGCCGATTGTGAACATGGACTACGTCGTGGGAGCCAGAAC

GTTCCGCAGAGAAAAGAGGGCCGAGCGTCTCACCTCGAGGGTGAAGGCACTGTT

CAGCGTGCTCAACTACGAGCGGGCGCGGCGCCCCGGCCTCCTGGGCGCCTCTGT

GCTGGGCCTGGACGATATCCACAGGGCCTGGCGCACCTTCGTGCTGCGTGTGCG

FIG.8C

GGCCCAGGACCCGCCGCCTGAGCTGTACTTTGTCAAGGTGGATGTGACGGGCGC

GTACGACACCATCCCCCAGGACAGGCTCACGGAGGTCATCGCCAGCATCATCAA

ACCCCAGAACACGTACTGCGTGCGTCGGTATGCCGTGGTCCAGAAGGCCGCCCA

TGGGCACGTCCGCAAGGCCTTCAAGAGCCACGTCTCTACCTTGACAGACCTCCA

GCCGTACATGCGACAGTTCGTGGCTCACCTGCAGGAGACCAGCCCGCTGAGGGA

TGCCGTCGTCATCGAGCAGAGCTCCTCCCTGAATGAGGCCAGCAGTGGCCTCTT

CGACGTCTTCCTACGCTTCATGTGCCACCACGCCGTGCGCATCAGGGGCAAGTC

CTACGTCCAGTGCCAGGGGATCCCGCAGGGCTCCATCCTCTCCACGCTGCTCTG

CAGCCTGTGCTACGGCGACATGGAGAACAAGCTGTTTGCGGGGATTCGGCGGGA

CGGGCTGCTCCTGCGTTTGGTGGATGATTTCTTGTTGGTGACACCTCACCTCAC

CCACGCGAAAACCTTCCTCAGGACCCTGGTCCGAGGTGTCCCTGAGTATGGCTG

CGTGGTGAACTTGCGGAAGACAGTGGTGAACTTCCCTGTAGAAGACGAGGCCCT

GGGTGGCACGGCTTTTGTTCAGATGCCGGCCCACGGCCTATTCCCCTGGTGCGG

CCTGCTGCTGGATACCCGGACCCTGGAGGTGCAGAGCGACTACTCCAGCTATGC

CCGGACCTCCATCAGAGCCAGTCTCACCTTCAACCGCGGCTTCAAGGCTGGGAG

GAACATGCGTCGCAAACTCTTTGGGGTCTTGCGGCTGAAGTGTCACAGCCTGTT

TCTGGATTTGCAGGTGAACAGCCTCCAGACGGTGTGCACCAACATCTACAAGAT

CCTCCTGCTGCAGGCGTACAGGTTTCACGCATGTGTGCTGCAGCTCCCATTTCA

TCAGCAAGTTTGGAAGAACCCCACATTTTTCCTGCGCGTCATCTCTGACACGGC

CTCCCTCTGCTACTCCATCCTGAAAGCCAAGAACGCAGGGATGTCGCTGGGGGC

FIG.8D

CAAGGGCGCCGCCGGCCCTCTGCCCTCCGAGGCCGTGCAGTGGCTGTGCCACCA
AGCATTCCTGCTCAAGCTGACTCGACACCGTGTCACCTACGTGCCACTCCTGGG
GTCACTCAGGACAGCCCAGACGCAGCTGAGTCGGAAGCTCCCGGGGACGACGCT
GACTGCCCTGGAGGCCGCAGCCAACCCGGCACTGCCCTCAGACTTCAAGACCAT
CCTGGACTGATGGCCACCCGCCCACAGCCAGGCCGAGAGCAGACACCAGCAGCC
CTGTCACGCCGGGCTCTACGTCCCAGGGAGGGAGGGGCGGCCCACACCCAGGCC
CGCACCGCTGGGAGTCTGAGGCCTGAGTGAGTGTTTGGCCGAGGCCTGCATGTC
CGGCTGAAGGCTGAGTGTCCGGCTGAGGCCTGAGCGAGTGTCCAGCCAAGGGCT
GAGTGTCCAGCACACCTGCCGTCTTCACTTCCCCACAGGCTGGCGCTCGGCTCC
ACCCCAGGGCCAGCTTTTCCTCACCAGGAGCCCGGCTTCCACTCCCCACATAGG
AATAGTCCATCCCCTGAT

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FIG.9A

HASGQRCVLLRTWEALAPATPAMPRAPRCRAVRSLLRSHYREVLPLATF
VRRLGPQGWRLVQRGDPAAFRALVAQCLVCVPWDARPPPAAPSFRQVSC
LKELVARVLQRLCERGAKNVLAFGFALLDGARGGPPEAFTTSVRSYLPN
TVTDALRGSGAWGLLLRRVGDDVLVHLLARCALFVLVAPSCAYQVCGPP
LYQLGAATQARPPPHASGPRRRLGCERAWNHSVREAGVPLGLPAPGARR
RGGSASRSLPLPKRPRRGAAPEPERTPVGQGSWAHPGRTRGPSDRGFCV
VSPARPAEEATSLEGALSGTRHSHPSVGRQHHAGPPSTSRPPRPWDTPC
PPVYAETKHFLYSSGDKEQLRPSFLLSSLRPSLTGARRLVETIFLGSRP
WMPGTPRRLPRLPQRYWQMRPLFLELLGNHAQCPYGVLLKTHCPLRAAV
TPAAGVCAREKPQGSVAAPEEEDTDPRRLVQLLRQHSSPWQVYGFVRAC
LRRLVPPGLWGSRHNERRFLRNTKKFISLGKHAKLSLQELTWKMSVRDC
AWLRRSPGVGCVPAAEHRLREEILAKFLHWLMSVYVVELLRSFFYVTET
TFQKNRLFFYRKSVWSKLQSIGIRQHLKRVQLRELSEAEVRQHREARPA
LLTSRLRFIPKPDGLRPIVNMDYVVGARTFRREKRAERLTSRVKALFSV
LNYERARRPGLLGASVLGLDDIHRAWRTFVLRVRAQDPPPELYFVKVDV
TGAYDTIPQDRLTEVIASIIKPQNTYCVRRYAVVQKAAHGHVRKAFKSH
VSTLTDLQPYMRQFVAHLQETSPLRDAVVIEQSSSLNEASSGLFDVFLR
FMCHHAVRIRGKSYVQCQGIPQGSILSTLLCSLCYGDMENKLFAGIRRD
GLLLRLVDDFLLVTPHLTHAKTFLRTLVRGVPEYGCVVNLRKTVVNFPV

FIG.9B

EDEALGGTAFVQMPAHGLFPWCGLLLDTRTLEVQSDYSSYARTSIRASL

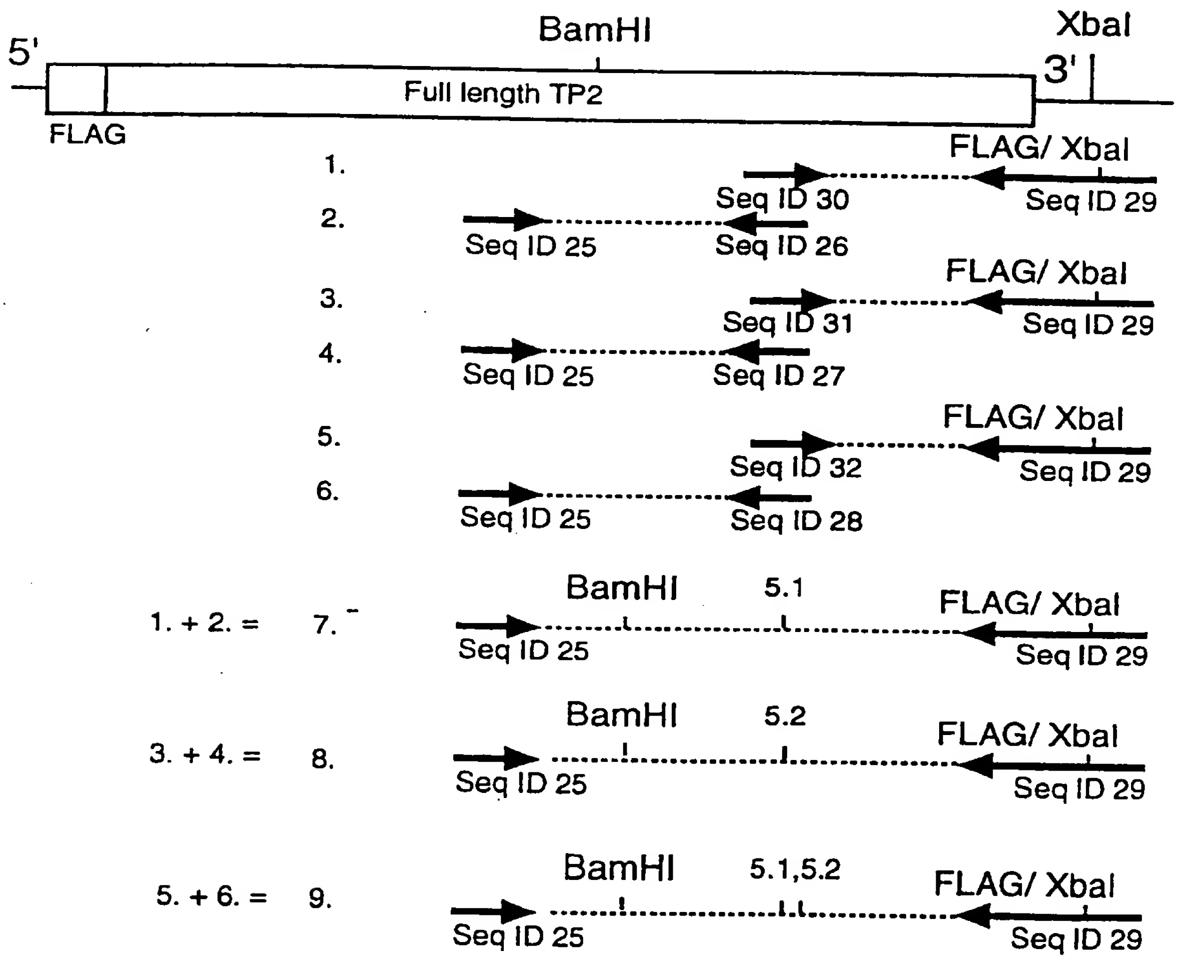
TFNRGFKAGRNMRRKLFGVLRLKCHSLFLDLQVNSLQTVCTNIYKILLL

QAYRFHACVLQLPFHQQVWKNPTFFLRVISDTASLCYSILKAKNAGMSL

GAKGAAGPLPSEAVQWLCHQAFLLKLTRHRVTYVPLLGSLRTAQTQLSR

KLPGTTLTALEAAANPALPSDFKTILD

FIG.10


BamHI
XbaI
5'
3'
Full length TP2
FLAG
1.
FLAG/ XbaI
Seq ID 30
Seq ID 29
2.
Seq ID 25
Seq ID 26
3.
FLAG/ XbaI
Seq ID 31
Seq ID 29
4.
Seq ID 25
Seq ID 27
5.
FLAG/ XbaI
Seq ID 32
Seq ID 29
6.
Seq ID 25
Seq ID 28
1. + 2. =
7.
BamHI
5.1
FLAG/ XbaI
Seq ID 25
Seq ID 29
3. + 4. =
8.
BamHI
5.2
FLAG/ XbaI
Seq ID 25
Seq ID 29
5. + 6. =
9.
BamHI
5.1,5.2
FLAG/ XbaI
Seq ID 25
Seq ID 29

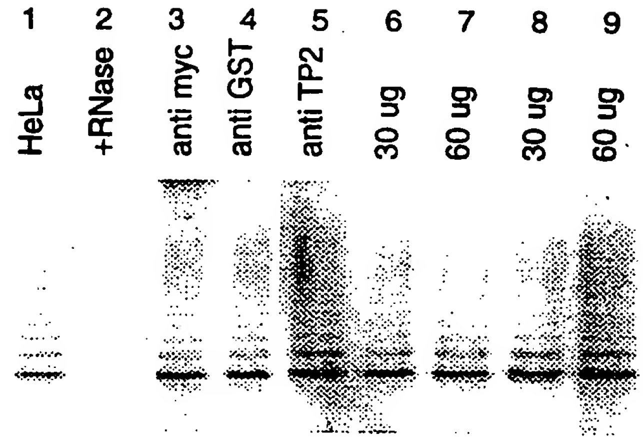


FIG.11A

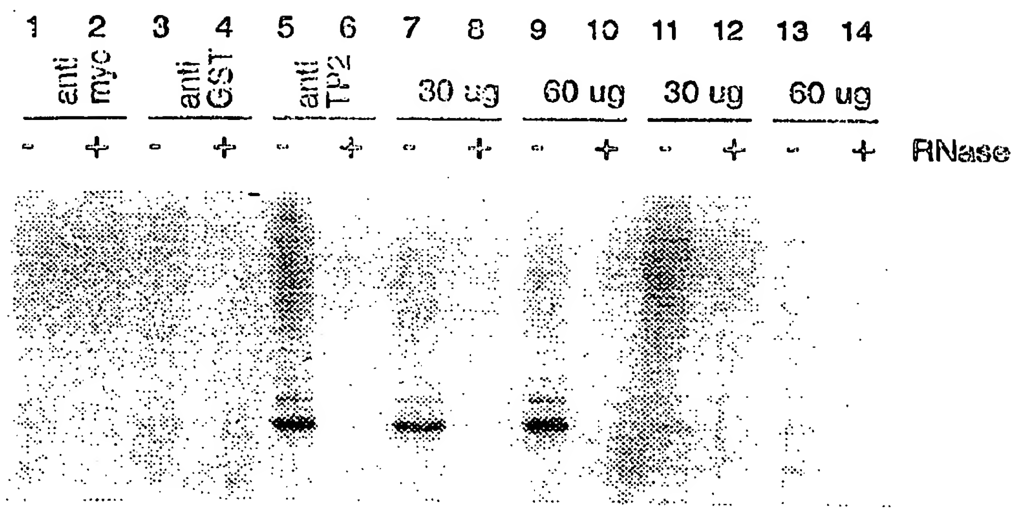


FIG.11B

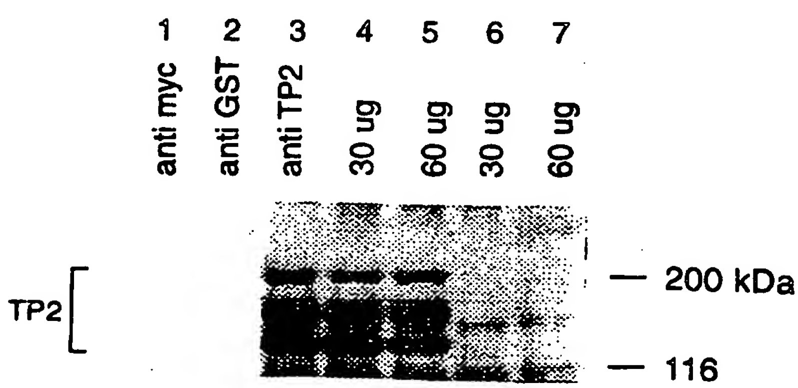


FIG.11C

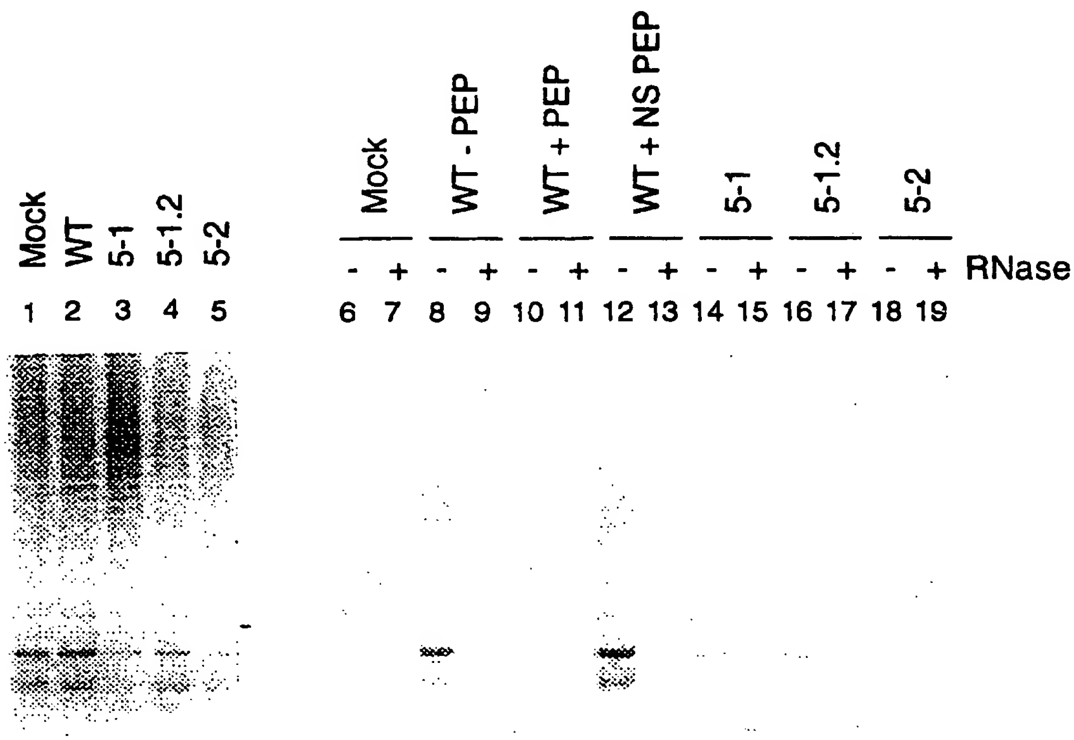


FIG.12A

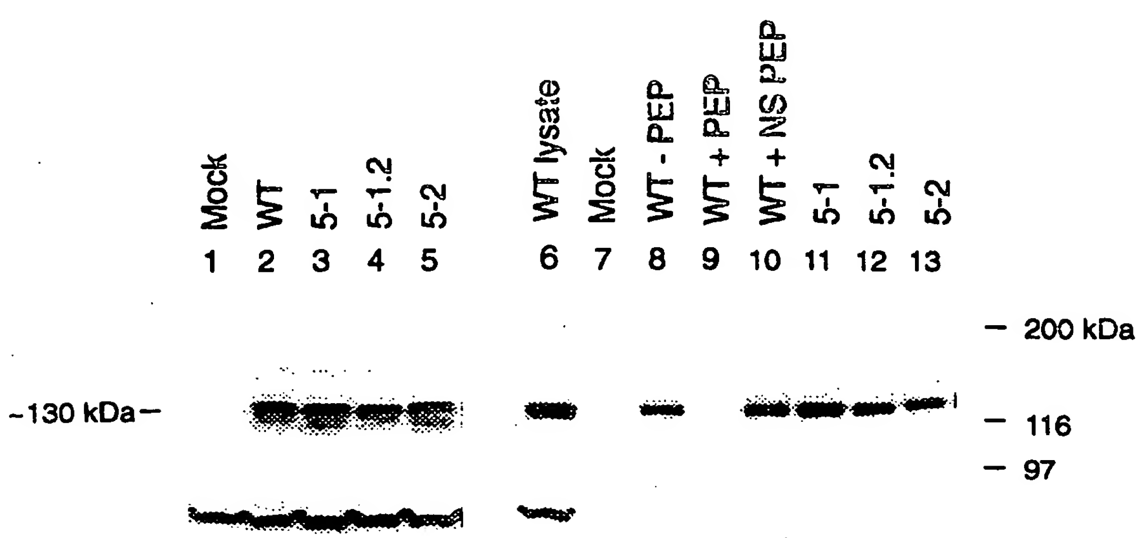


FIG.12B

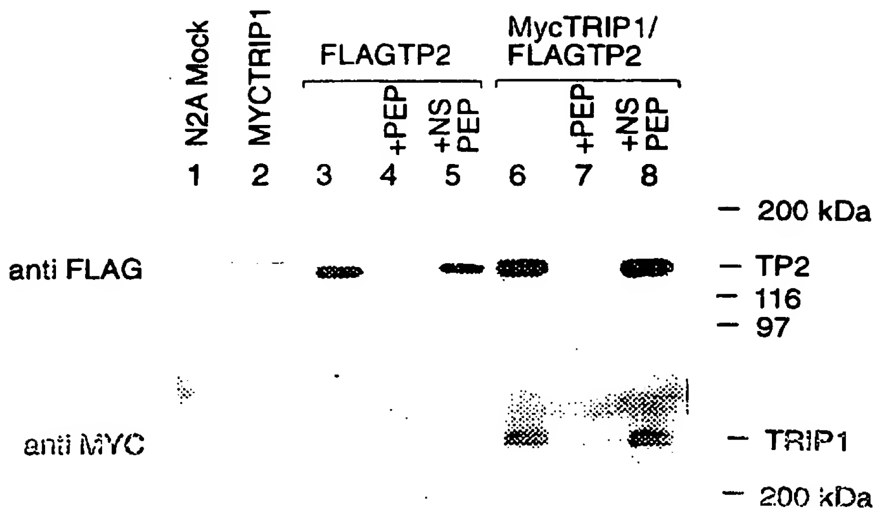


FIG.13A

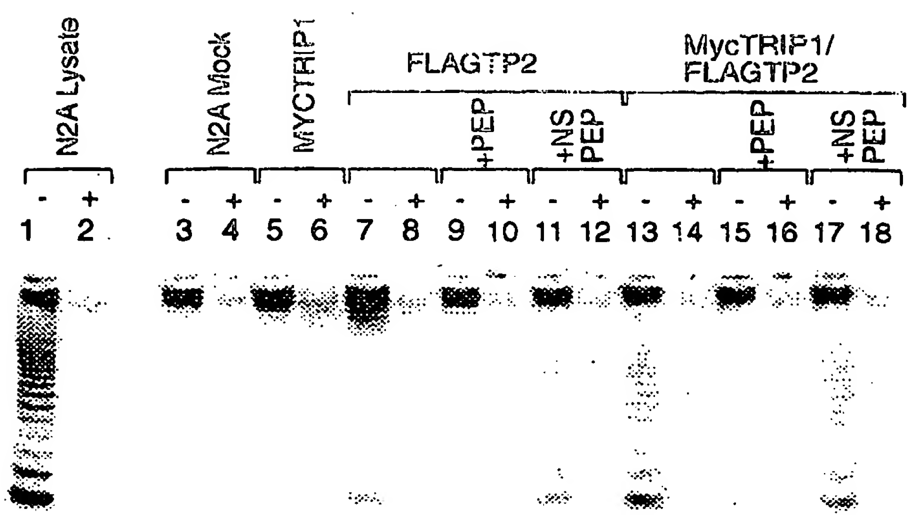
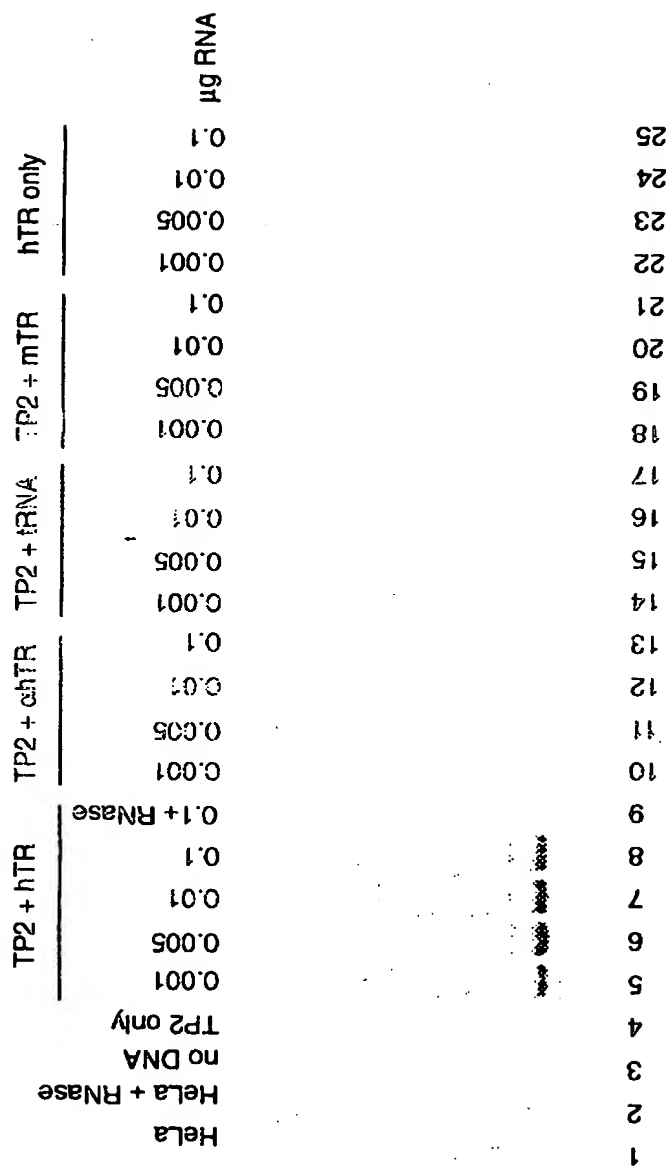


FIG.13B


µg RNA
hTR only
TP2 + mTR
TP2 + tRNA
TP2 + αhTR
TP2 + hTR
HeLa
HeLa + RNase
no DNA
TP2 only
0.001
0.005
0.01
0.1
0.1 + RNase
1
2
3
4
5
6
7
8
9
10
11
12
13
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24
25

FIG. 14

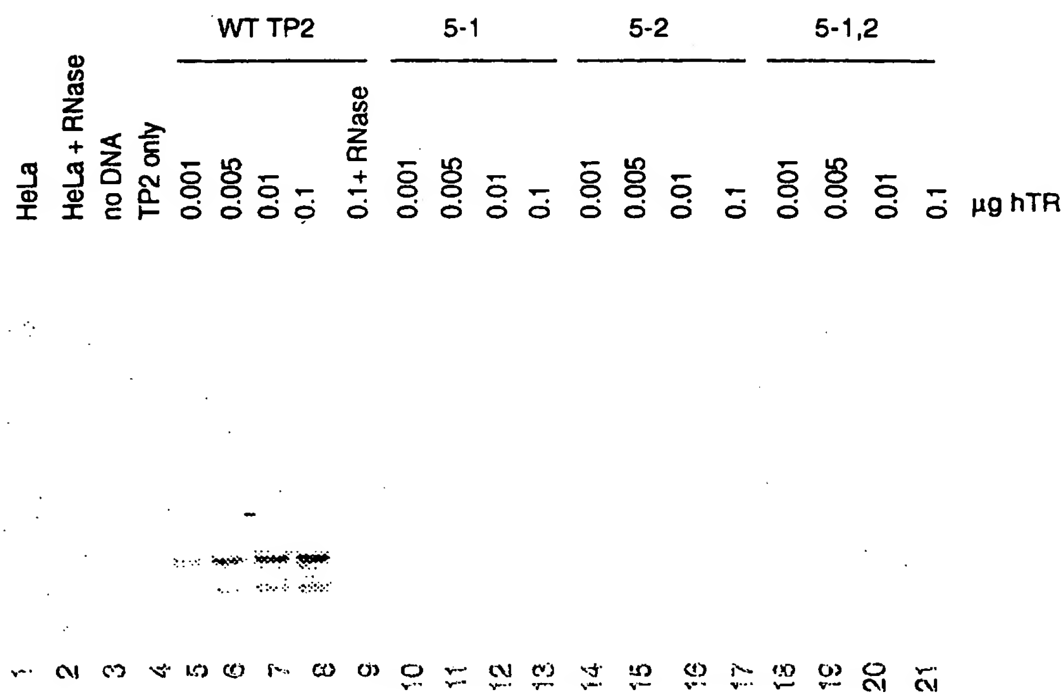

FIG. 15A

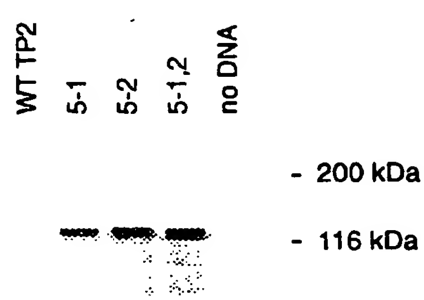

FIG. 15B

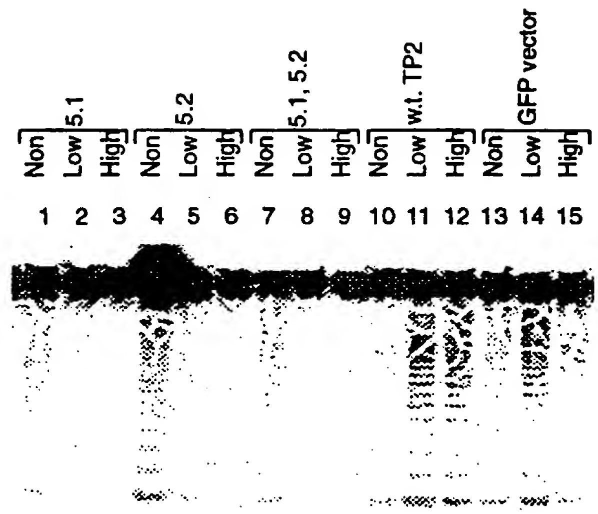

FIG.16A

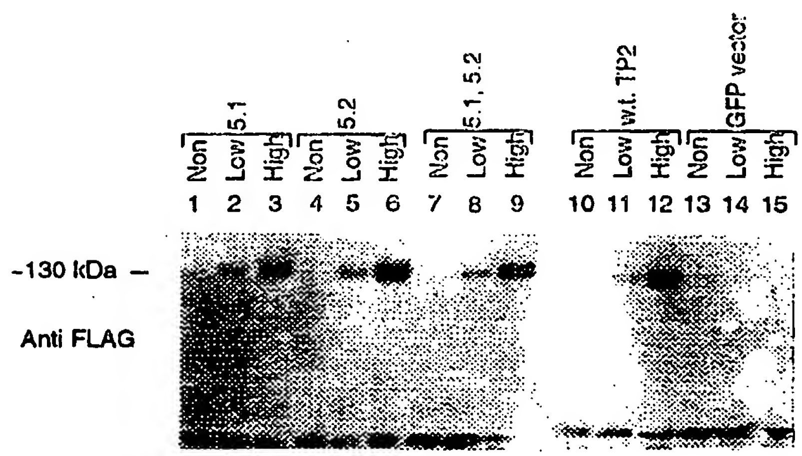

FIG.16B

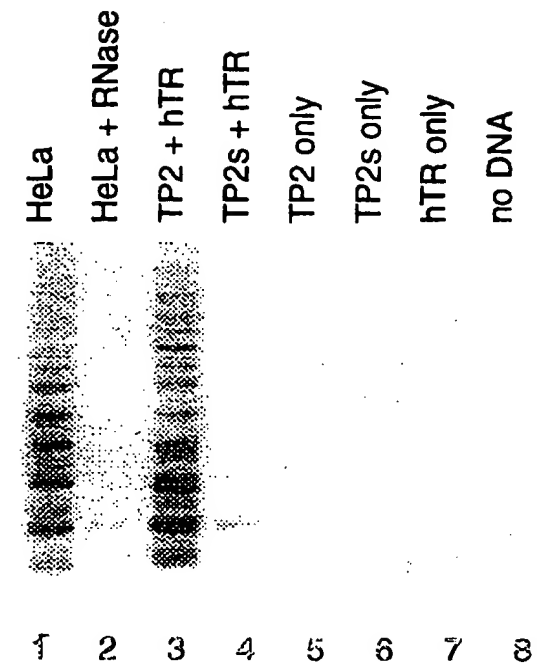

FIG.17A

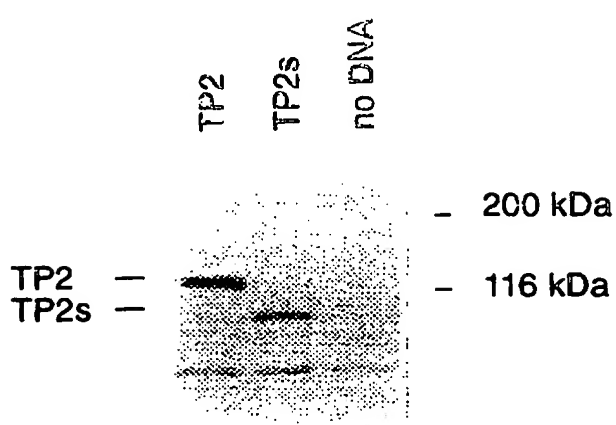

FIG.17B

TP2+hTR

no DNA -TP1 + TP1

1 2 1 2 1 2 µL assayed

1 2 3 4 5 6

FIG.18